A Medical Audit of the Management of Cryptococcal Meningitis in HIV patients in the Cape Winelands (East) District, Western Cape, South Africa.

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Declaration

I, the undersigned, hereby declare that the work contained in this assignment is my original work and that I have not previously submitted it, in its entirety or in part, at any university for a degree.

Signature: **.....….….....** **Date:** 24 August 2010

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11. Addenda

Abstract (English)

Introduction:

This thesis summarises the findings of a medical audit on the management of Cryptococcal Meningitis (CM). The study population of HIV positive adults (N = twenty five) were admitted during November 2009 – June 2010 to five hospitals of the Cape Winelands (East) District, Western Cape, South Africa.

In the context of the HIV pandemic, CM has become the most common cause of community-acquired meningitis, and has poor outcomes if left untreated. The South African HIV Clinician Society has published treatment guidelines in 2007. These guidelines have been used by the audit team to compile a list of measurable criteria (with set targets) to evaluate the structure, process and outcome of CM management. A pilot audit (2008) at the regional hospital has demonstrated that certain target standards were not met.

Aims and Objectives:

The aim was to improve the quality of the clinical care of HIV-patients diagnosed with CM in the Cape Winelands (East) district. The objectives included the review of the audit criteria and target standards, demonstrating improvement in quality of CM care at the Level 1 and 2 hospitals, identifying new interventions based on the findings and providing recommendations to the health facilities.

Methods

In 2009, the researcher formed a new audit team, reviewed the audit criteria and held teaching interventions based on the national treatment guidelines. An intervention, based on the findings of the pilot audit, aimed at improving the clinical team's adherence to the treatment guidelines.

Results

The audit identified the following areas that did not meet the target standards: the availability of Amphotericin B (Ampho B) and spinal manometers; the use of manometry in all initial lumbar punctures (LPs); completing fourteen days of the required Ampho B treatment; renal monitoring in patients on Ampho B; commencement of antiretroviral treatment (ART) by week four; and, the two-month survival figures post-diagnosis.

The re-audit at the Level 2 hospital highlighted the need for improved medical record keeping to aid the audit process. Arrangement of inpatient ART counselling happened more consistently at the Level 1 hospitals. Adherence to the ART target and measures to prevent Ampho B related morbidity is comparable to that of the Level 2 hospital. The audit has also provided insight to the researcher and audit team on the practical challenges of conducting a prospective data collection technique across different care settings.

Recommendations

Level 1 hospitals should continue to manage CM patients. The availability of spinal manometers and closer adherence to renal monitoring require attention. Formal feedback to the audit team and clinical teams is planned. A multimodal interdisciplinary Quality Improvement approach (such as an integrated care pathway) is recommended and a future re-audit is encouraged to assess improved adherence to the CM management guidelines. The buy-in of stakeholders (management, health care workers and patients), the ongoing support of an audit team and a committed Quality Improvement environment will allow the medical audit process to become ingrained in the South African public healthcare setting.

Opsomming (Afrikaans)

Inleiding

Hierdie tesis bied ‘n opsomming van die sleutelbevindinge van ‘n mediese oudit van Cryptokokkale Menigitis (CM) sorg. Die studie groep van MIV-positiewe volwassenes (N = vyf-en-twintig) het binne-pasiënt behandeling ontvang gedurende November 2009 tot Junie 2010 in vyf hospitale van die Kaapse Wynland (Oos) distrik.

In die konteks van die MIV pandemie het CM die mees algemene oorsaak van gemeenskapsverworwe meningitis geword, en het swak uitkomste indien onbehandeld. Die Suid-Afrikaanse HIV Clinici Vereniging het in 2007 behandelingsriglyne gepubliseer. Hierdie riglyne het die oudit span gebruik om ‘n lys van meetbare kriteria (met teiken standaarde) saam te stel om die struktuur, proses en uitkoms fasette van CM sorg te evalueer. ‘n Proef oudit (2008) by die streekshospitaal het getoon dat sekere teiken standaarde nie behaal was nie.

Doelstelling

Die doelstelling was om die kwaliteit van kliniese sorg van MIV-pasiënte met CM (in die Kaapse Wynland (Oos) distrik) te verbeter. Die doelstelling sluit in die hersiening van die oudit kriteria, die bevesting van verbetering in kwaliteit CM sorg by vlak 1 en 2 hospitale, identifisering van nuwe ingreep-moontlikhede gebaseer op die bevindinge en die verskaffing van toepaslike aanbevelings aan die gesondheidsorg fasiliteite.

Metodes

Die navorser het in 2009 ‘n nuwe oudit span gevorm, die oudit kriteria hersien en opleidingsingrepe geskoei op die nasionale riglyne gefasiliteer. Opleidingsingrepe, gebaseer op bevindinge van die proef oudit, het ten doel gehad dat die kliniese span die nasionale riglyne nakom.

Resultate

Die oudit het die volgende areas uitgelig waar daar nie aan die teikenstandaarde voldoen was nie: the beskikbaarheid van Amphotericin B (Ampho B) en spinale manometers; die gebruik van manometrie in alle aanvanklike lumbaal punksies (LPs); voltooi van die veertien dae Ampho B

behandelingsteiken; nierfunksie monitoring van pasiënte op Ampho B; aanvang van anti-retovirale behandeling teen week vier; en, die twee maande oorlewing post-diagnose syfers.

Die opvolg oudit by die vlak 2 hospitaal bevestig die belang van verbeterde kliniese notas om die oudit proses te vergemaklik. Die reël van binne-pasiënt ART berading gebeur meer bestendig in Vlak 1 hospitale. Bereiking van die ART teiken en maatreëls om Ampho B verwante morbiditeit te voorkom, is vergelykbaar met die bevindinge by die vlak 2 hospitaal. Die oudit het die navorser en die oudit span ingelig rakende die praktiese uitdagings om ‘n prospektiewe data insamelingsmetode te poog in verskillende kliniese kontekste.

Aanbevelings

Vlak 1 hospitale kan steeds CM pasiënte versorg. Die beskikbaarheid van spinale manometers en deeglike nierfunksie monitering sal die behaling van teiken standaarde vergemaklik. Formele terugvoer aan die oudit span en kliniese span word beoog. ‘n Multimodale interdissiplinêre Kwaliteitsverbeterings benadering (soos ‘n geïntegreerde sorgplan) word aanbeveel en ‘n toekomstige oudit word aangemoedig om verbetering in toepassing van die CM riglyne te evalueer. Dit is belangrik om die sleutelspelers (bestuur, gesondheidswerkers en pasiënte) te betrek. Verder word voortgesette ondersteuning van die oudit span en ‘n toegewyde omgewing van kwaliteitsverbetering aanbeveel. Sodoende sal die oudit proses in Suid-Afrikaanse publieke sorg geintegreer word.

List of Abbreviations

- AIDS: Acquired Immune Deficiency Syndrome
- ASSA: Actuarial Society of South Africa
- Ampho B: Amphotericin B
- ART: Anti-Retroviral Treatment
- BH: Brewelskloof Hospital
- CD4: Cluster of Differentiation 4 (glycoprotein found on the surface of helper T cells)
- CLAT: Cryptococcal Latex Agglutination Test
- CH: Ceres Hospital
- CM: Cryptococcal Meningitis
- CMA: Cryptococcal Meningitis Audit
- CQI: Continuous Quality Improvement
- CSC: Centre for Statistical Consultation, Stellenbosch University
- CSF: Cerebrospinal Fluid
- CT: Computer Tomography
- EBM: Evidence-based Medicine
- HIV: Human Immunodeficiency Virus
- HREC: Human Research Ethics Committee
- HRSA: Health Resources and Services Administration

- iCP: (Integrated) Care Pathway
- ICP: Intracranial Pressure
- ID clinic: Infectious Diseases clinic
- IDSA: Infectious Diseases Society of America
- IRIS: Immune Reconstitution Inflammatory Syndrome
- IV: Intravenous
- MDR: Multi-drug Resistant
- NHLS: National Health Laboratory Service
- NYSDOH AI: New York Department of Health AIDS Institute
- OI: Opportunistic Infection
- OP: Opening Pressure
- PEPFAR: United States President's Emergency Plan for AIDS Relief
- PTC: Pharmaceutical Treatment Committee
- QI: Quality Improvement
- QOC: Quality of Care
- RH: Robertson Hospital
- SA: South Africa
- TB: tuberculosis
- U&E, Mg: Urea, Creatinine and Electrolytes, Magnesium

- UNAIDS: Joint United Nations Programme on HIV/AIDS
- UNICEF: United Nations Children's Fund
- USA: United States of America
- WH: Worcester Hospital
- WHO: World Health Organisation

Please note the following definitions refer to the hospital level of care and associated package of care (as defined by the Department of Health, South Africa):

Level 1 = District hospital

Level 2 = Regional hospital

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1. Introduction

1.1 Introducing Medical Audit and Quality Improvement

A few thoughts on Quality, Change and Life:

"Quality is never an accident; it is always the result of high intention, sincere effort, intelligent direction and skillful execution; it represents the wise choice of many alternatives." – William A Foster. [1]

"Quality is the result of a carefully constructed cultural environment. It has to be the fabric of the organization, not part of the fabric." – Phillip Crosby. [2]

"Quality is everyone's responsibility." – W Edwards Deming. [3]

"What we achieve inwardly will change outer reality." – Plutarch, *c* 46 – 120 AD. [4]

"The most important part of the audit cycle is making change" – Baker, quoted in a Clinical Audit Study Guide of the Sussex Partnership NHS trust. [5]

"As is a tale, so is life: not how long it is, but how good it is, is what matters." – Seneca the Younger, *c* 3 BC – 65 AD. [4]

Medical Audit, also known as Clinical Audit and Quality Improvement (QI) Cycle, is the centre of the process of Continuous Quality Improvement (CQI). Quality of Care (QOC) is one of the pillars of Clinical Governance, the concept that refers to the accountability of a health care system for ensuring the correct standard of care provided to its patients. [6]

The net value of the audit process is that it leads to a review of clinical decision-making and, ultimately, to a shift in focus: making the most efficient use of resources for the patient. This viewpoint supports the role of quality improvement in resource-constrained settings.

1.2 Introducing the setting of this audit

This medical audit focused on HIV (Human Immunodeficiency Virus)-positive adult patients treated for Cryptococcal Meningitis (CM) at hospitals in the Cape Winelands (East) district, Western Cape Province, South Africa.

Figure 1 and 2 provide geographical orientation to the Cape Winelands district and its sub-districts.

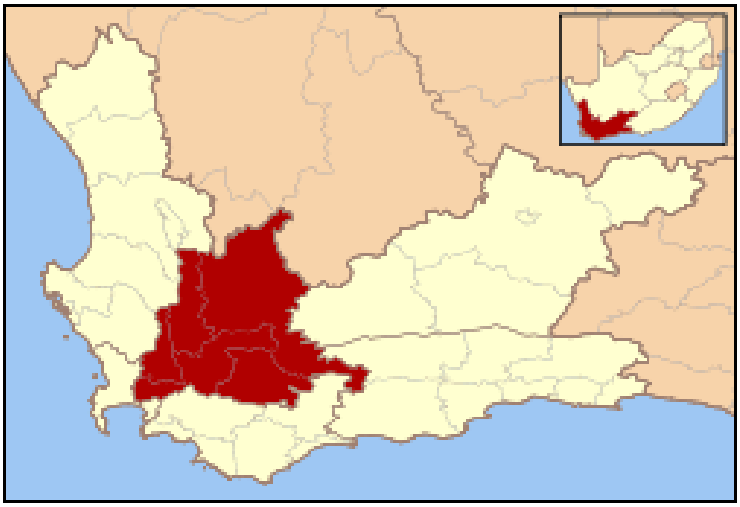


Figure 1.
The Cape Winelands district, Western Cape Province [7]

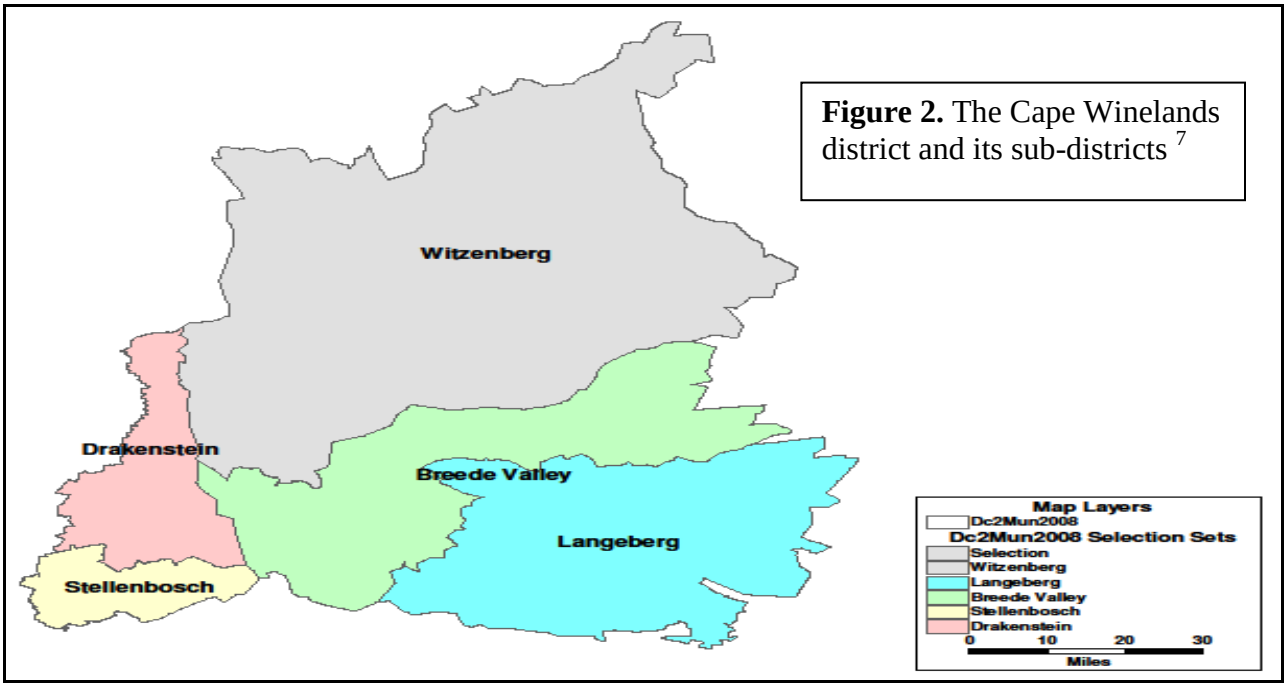


Figure 2. The Cape Winelands district and its sub-districts [7]

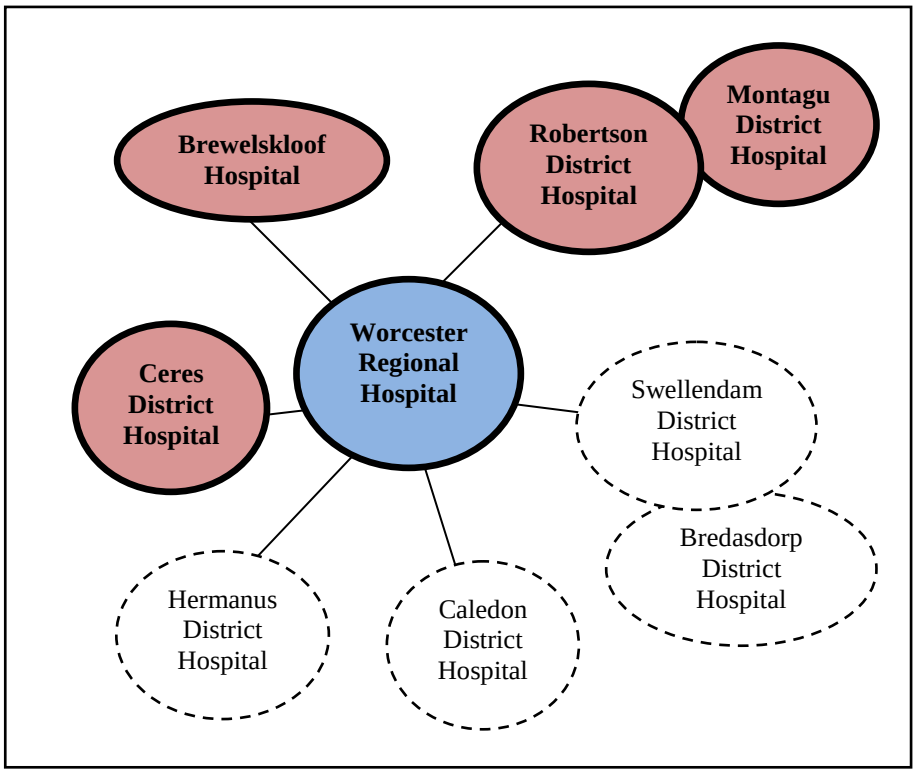


Figure 3: Schematic overview of the Worcester Hospital Referral Network

(Based on a schematic overview [8])

Figure 3 provides a schematic overview of all the Level 1 hospitals (district hospitals) that refer to Worcester regional hospital (Level 2). It is important to note that there are two regional hospitals in the Cape Winelands district: Paarl regional hospital (in Drakenstein sub-district) serves the Drakenstein and Stellenbosch sub-districts (Cape Winelands: West). The Cape Winelands (East) district refers to the three sub-districts that are served by Worcester regional hospital: Witzenberg (Ceres hospital), Breede Valley (Worcester regional hospital and Brewelskloof Tuberculosis hospital) and Langeberg (Robertson and Montagu hospitals).

1.2.1 Worcester regional hospital (WH), is situated in the Breede Valley sub-district (population: 148 623 in October 2009). Worcester hospital (266 beds) provides specialist services to seven Level 1 hospitals and numerous primary health care facilities of two health districts, Cape Winelands and Overberg. The Overberg district (Hermanus, Caledon, Swellendam and Bredasdorp) does not have its own regional hospital and, therefore, uses Worcester as its referral hospital. [9,10]

1.2.2 Brewelskloof hospital (BH), Worcester, is a specialised tuberculosis (TB) hospital (both adults and children) for the Cape Winelands and Overberg districts and is one of six TB hospitals of the Western Cape. There are 206 beds for TB patients. This hospital is the designated multi-drug resistant (MDR) TB specialist centre. Four to five specialist TB doctors manage the TB patients in sub-acute beds with longer inpatient time than the acute beds found in the district and regional hospitals.

Admission criteria for Brewelskloof hospital are those diagnosed patients who:

- "are too ill to take medication at the local clinic
- experience side effects of TB drugs
- have resistant strains of TB
- need injections and cannot receive it on a daily basis locally
- have a history of defaulting treatment
- have poor social circumstances, especially children in this situation" [11]

Due to the co-morbidity of HIV and TB, many of the patients admitted for TB treatment develop opportunistic infections (OIs) associated with World Health Organisation (WHO) stage four HIV disease. CM, an example of an OI, is also managed in the TB wards.

Worcester hospital's Family Medicine and Internal Medicine departments use one of Brewelskloof hospital's wards for inpatient care (rehabilitation beds, step-down beds and Level 1 beds). Typically, CM patients diagnosed at Worcester hospital are admitted for inpatient care in this combined ward at Brewelskloof hospital. Doctors from Worcester hospital are responsible for the inpatient care of these patients.

1.2.3 The Cape Winelands (East) district has three Level 1 hospitals:

- Ceres hospital (CH) serves the Witzenberg sub-district (population: 100 939 in October 2009). The hospital (76 beds) has six generalist doctors.
- Robertson hospital (RH) and Montagu hospital (MH) serve the Langeberg sub-district (population: 102 097 in October 2009). RH (46 beds) has six generalist doctors and MH (40 beds) has two generalist doctors. [7]

1.2.4 The burden of HIV disease in the Cape Winelands, Western Cape and South Africa is presented:

- The South African National HIV Survey demonstrated an estimated HIV prevalence in 2008 in the Western Cape of 3.8% (South African national prevalence estimated at 10.9% in 2008). [12]
- The South African Department of Health Study (2007) found an estimated HIV prevalence among antenatal clinic attendees in the Western Cape of 12.6% (South African national prevalence estimated at 28%). [12]
- The UNAIDS/WHO report published in July 2008 estimated a HIV prevalence of 18.1% in those aged 15-49 years old at the end of 2007 (high and low estimates: 15.4% and 20.9% respectively). This implies that around 5.7 million South Africans were living with HIV at the end of 2007, including 280,000 children under 15 years old. [12]
- The ASSA2003 (Actuarial Society of South Africa) model produced a similar estimate than the UNAIDS/WHO report: 5.4 million people living with HIV in mid-2006, or around 11% of the total population. This model predicts that the number will exceed 6 million by 2015, by which time an estimated 5.4 million South Africans will have died of AIDS. [12]

1.2.5 The June 2010 data of total patients on Anti-Retroviral Treatment (ART) for each sub-district of the Cape Winelands (East) district:

- Breede Valley: Total Adults = 1996; Total Children = 170; Total = 2166.
- Witzenberg: Total Adults = 1031; Total Children = 31; Total = 1061.
- Langeberg: Total Adults = 575; Total Children = 40; Total = 615. [13]

In summary, CM patients are admitted for inpatient care at the hospitals of the Cape Winelands (East) district. This inpatient phase is required for Amphotericin B treatment. On discharge, these patients are managed at various ART sites and primary health care clinics in the drainage area of these hospitals. Generalist medical practitioners staff these facilities (except for the regional hospital and TB hospital).

1.3 Introducing Cryptococcal Meningitis

Cryptococcal Meningitis (CM) is caused by an opportunistic encapsulated yeast, *Cryptococcus neoformans*. Cryptococcosis refers to a disseminated infection (skin, lung, meninges). Despite recent expansion of Anti-Retroviral Treatment (ART) programmes in developing countries, cryptococcosis remains a major opportunistic pathogen and a leading cause of mortality in AIDS patients (HIV infection causes a defective T-cell-mediated immunity, which leads to opportunistic infections). [14]

CM has become the leading cause of community-acquired meningitis (ahead of tuberculous and bacterial meningitis) and has a significant mortality if not treated correctly (especially in the first two weeks after diagnosis). CM accounts for 20–45% of laboratory-confirmed cases of meningitis in Southern Africa. [15]

The researcher conducted an initial pilot audit (retrospective) at Worcester hospital in 2008 as part of an assignment for the M Med (Family Medicine) degree. The results showed areas requiring improvement in the management of CM cases at Worcester hospital. The audit team identified gaps in the knowledge of the health care professionals, especially regarding the diagnosis and management of raised intracranial pressure (see summary of results in Addendum B). These conclusions and recommendations are applicable to CM management in the district (by extrapolation). These are the highlights of the findings from the pilot audit:

- Fourteen patients' records were reviewed and assessed according to target standards set by the audit team
- Target standards for completing 14 days of Amphotericin B and 8 weeks of high dose Fluconazole were met in this period (June 2007 until July 2008)
- Opening pressures (manometry) with lumbar punctures were done in only 3 out of the 14 patients
- No cases of Amphotericin B associated renal impairment were found (adequate IV Saline pre-hydration should prevent this adverse event)
- All the patients were referred for ART commencement, but none of the patients was commenced by the target standard (4 weeks from onset of antifungal treatment).
- Adherence to long term Fluconazole prophylaxis was below target standard

By involving the medical team (doctors and nurses of the hospitals involved in the audit) in implementing the national guidelines on CM management, the researcher and the audit team aimed to achieve the following:

- increased adherence to national guidelines, which will in effect lead to improved Quality of Care (QOC)
- increased survival
- effective diagnosis and treatment of CM-associated raised intracranial pressure (increased measurement of CSF opening pressures)
- early access to ART
- correct administration of Amphotericin B
- improved morale of staff, patients and relatives dealing with CM

2. Literature Review

2.1 Literature Review of Cryptococcal Meningitis

2.1.1 Importance and relevance of CM as a clinical topic

Cryptococcal Meningitis (CM) is now the leading cause of community-acquired meningitis, ahead of tuberculous and bacterial meningitis. It accounts for 20–45% of laboratory-confirmed cases of meningitis in Southern Africa. [15]

A 2009 article looked at the global burden of CM: the incidence ranged from 0.04 to 12% per year among persons living with HIV. Sub-Saharan Africa had the highest yearly burden estimate (median incidence 3.2%, 720 000 cases; range, 144 000–1.3 million). [16]

In a review in India, the authors note that CM is the first opportunistic infection that occurs in over a quarter of patients who develop AIDS. Furthermore, about 5–10% of patients with AIDS (CD4 lymphocyte count of <200 cells/ml) develop CM. About three quarters of patients have a large burden of fungal organisms, evidenced by a heavily positive Cerebrospinal Fluid (CSF) Indian ink preparation and very high titers of cryptococcal antigen in blood and CSF. [17]

2.1.2 CM is an AIDS-defining disease with significant mortality

A Ugandan article discussed the outcomes in CM management in the pre- and post-ART era, comparing the outcomes of North America with those of sub-Saharan Africa. The North American mortality rate for CM was less than 10% with administration of a combination of Amphotericin B (0.7–1.0 mg/kg per day), Flucytosine, and aggressive management of increased intracranial pressure. However, the mortality rate at 14 days in sub-Saharan Africa after receipt of Amphotericin B ranged from 17% to 36%, with a median duration of survival of about 1 month. The risk factors identified for increased mortality include delay in diagnosis, lack of Amphotericin B treatment, lack of ART, and greater fungal burdens. Furthermore, Fluconazole alone is routinely used in Africa because of its affordability and ease of use. However, treatment of HIV-associated CM in an African setting with

Fluconazole only (without Amphotericin B and ART) had a poor survival rate of less than 5% at 6 months. [18]

The article on global CM burden quoted an estimated case fatality of 55% in regions with primarily less developed countries, excluding sub-Saharan Africa, where it was estimated to be 70%. [16]

2.1.3 South African National Guidelines for CM treatment and the importance of initial acute treatment phase

The Spring 2007 edition of *The South African Journal of HIV Medicine* provided *Guidelines for the Prevention, Diagnosis and Management of Cryptococcal Meningitis and Disseminated Cryptococcosis in HIV-infected patients*. The authors stressed the importance of improving the initial acute management of CM, as this will maximize the patient's chances of initial survival and subsequent entry into the ART programme. [19]

The guideline committee recommended the following treatment protocol for CM in HIV-infected patients:

A. Completion of 14 days of the fungicidal agent, Amphotericin B (at 1mg/kg/day) (the intensive phase of CM management)
B. Completion of 8 weeks of high dose treatment (400mg daily) of the fungistatic agent, Fluconazole (the consolidation phase of CM management)
C. Long-term use of Fluconazole at 200mg daily (secondary prophylaxis)
D. Measurement of opening pressures when doing Lumbar Punctures (LPs), to detect raised intracranial pressure (more than 20 cmH_2O) and to relieve pressure with therapeutic taps
E. Arranging a CT scan of the brain if there are focal signs, depressed level of consciousness or other contra-indications for a LP.

2.1.4 Best CM treatment options in South Africa

A comprehensive Cochrane review by South African authors investigated the best treatment for CM in resource-limited settings. Usually only Amphotericin B and Fluconazole are available in these settings. The authors were unable to recommend either Amphotericin B or Fluconazole as the superior drug for CM, as they could find no suitable studies in which

these two drugs were compared. Future research into the management of CM should focus on the most effective use of medications that are available in resource-limited settings. It was noted that Flucytosine in combination with Amphotericin B leads to faster and increased sterilisation of CSF compared to using Amphotericin B alone. However, Flucytosine is not available in many developing countries, including South Africa. The authors recommend that policy makers and national departments of health in these countries should consider procuring this drug for HIV treatment programmes. [20]

A 2008 review described studies that have started to optimise antifungal regimens and address the complications of raised cerebrospinal fluid pressure and cryptococcal IRIS. Furthermore, Amphotericin B at 1 mg/kg per day has been shown to be more rapidly fungicidal than the standard dose of 0.7 mg/kg per day (currently used in many SA hospitals). New data support the importance of combination therapy with Flucytosine. Amphotericin B and Fluconazole at 800mg is an alternative combination that appears superior to Amphotericin B alone. At a dosage of 400mg per day, Fluconazole alone is much less rapidly fungicidal than Amphotericin B and is associated with the development of secondary resistance. [14]

2.1.5 Prevention of Amphotericin B associated renal impairment and electrolyte disturbance

The guidelines in the SA Journal of HIV Medicine recommend prehydration with normal saline (containing added potassium) to prevent Amphotericin B-associated nephrotoxicity (usually occurring in the second week of therapy) and electrolyte abnormalities. Baseline and twice-weekly monitoring of creatinine, potassium and magnesium is appropriate. If the creatinine level doubles, one should consider omitting a dose of Amphotericin B or increasing prehydration to one litre eight-hourly. However, if the creatinine level remains elevated, one should stop Amphotericin B and use Fluconazole alone. [19]

2.1.6 Importance of diagnosing and treating CM-associated raised intracranial pressure

A seminal article, referred to as the “Graybill Paper”, highlighted the importance of raised intracranial pressure in CM. In this study, patients with opening pressures >25 cm H_2O were associated with higher titers of cryptococcal capsular polysaccharide antigen in CSF, more

frequently positive Indian ink smears of CSF and more frequent headache, meningism, papilloedema, hearing loss, and pathological reflexes. Patients with pretreatment opening pressure <25 cm H_2O had increased short-term survival compared with those with higher pressure. The authors conclude that opening pressures >25 cm H_2O should be treated with large-volume CSF drainage. [21]

A study published in 2009 (set in Thailand and South Africa) highlights the necessity of access to manometers to enable diagnosis and treatment of raised pressures. The authors conclude that aggressive management of raised opening pressure through repeated CSF drainage appeared to prevent any adverse impact of raised opening pressure on outcome in patients with CM. Their results support increasing access to manometers in resource-poor settings and routine management of opening pressure in patients with CM. [22]

2.1.7 Optimal timing of ART initiation

Evidence for the optimal timing of ART requires further research. The 2008 review noted that early mortality in developing countries is exceptionally high in those patients awaiting commencement of ART, or in those recently started on ART. Their data, coupled with evidence from a randomized trial of immediate vs. deferred ART in the setting of acute AIDS-related opportunistic infections (13% of which were CM), argue for earlier ART. [14]

The treatment guidelines from the SA Journal of HIV Medicine noted that there is limited evidence for the optimal timing of ART initiation. The guideline committee believes that ART should be started 2 – 4 weeks after commencing treatment for CM. Although no prospective evidence existed in this regard, they felt that delaying ART introduction beyond 4 weeks to reduce the risk of IRIS may increase the risk of mortality in these patients with advanced immunosuppression. The long in-hospital stay associated with Amphotericin B therapy should be used to facilitate pre-ART counselling, identification of a treatment supporter and early referral to an ART clinic. [19]

2.1.8 CM management in the context of the EDL and Package of Care for Level 1 and Level 2 hospitals

The 2006 edition of *Standard treatment guidelines and Essential Drugs List for South Africa – Hospital Level, Adults* describes the management of Cryptococcosis in section 10.1.2 (p. 168). [23] The importance of therapeutic lumbar punctures in managing elevated intracranial pressure is emphasised. Patients with focal neurological signs require referral for specialist evaluation at the next level of care (Level 2). Amphotericin B is available on the District Hospital Code List. This indicates that the setting of a Level 1 hospital is appropriate for CM management (antifungal drugs are available).

In summary, the literature review showed that CM is the most common cause of meningitis in SA. At least 50% of CM cases have raised intracranial pressure on diagnosis. Effective treatment of increased pressure can improve outcome. The SA HIV Society Guidelines recommend the initiation of ART within two to four weeks from start of antifungal treatment for CM. The first two weeks are the most important phase of the treatment of CM, as this period has the biggest impact on outcome.

2.2 Literature Review: Medical Audit and Quality Improvement

Medical Audits (also called Clinical Audits) and Evidence Based Medicine (EBM) share a common history. "EBM is the explicit use of the best available evidence to inform decisions about the care of individual patients. ... QI (Quality Improvement) research seeks to implement in routine practice the processes and outcomes of care established by the best available evidence." [24]

The following definition of clinical (medical) audit is endorsed by the National Institute of Clinical Excellence (NICE), United Kingdom:
"Clinical audit is a quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change. Aspects of the structure, processes, and outcomes of care are selected and systematically evaluated against explicit criteria. Where indicated, changes are implemented at an individual, team, or service level and further monitoring is used to confirm improvement in healthcare delivery." [25]

Importantly, the audit forms part of a continuous process. A cycle or spiral illustrates the process of a medical audit. An appropriate climate or environment that supports the idea of "change for the better" is needed in order for this process to succeed. This necessitates the buy-in of key stakeholders: the public/patients, the clinical personnel and the health system management. A paradigm shift is required in terms of the climate of the organisation or health system: from a "culture of blame" to a culture where the best quality of care for the patient is sought, without fear of retribution or victimisation. [26]

A landmark report, *The Report of the Public Inquiry into Children's Heart Surgery at the Bristol Royal Infirmary 1984-1995*, was "written as a demand, on the behalf of patients, for change in the culture of the Service both within the NHS (National Health Service, United Kingdom) itself - how professionals behave towards each other - and also in the way that individual professionals treat their patients". This report argued for a change in organisational culture: "The culture of the future must be a culture of safety and of quality; a culture of openness and of accountability; a culture of public service; a culture in which collaborative teamwork is prized; and a culture of flexibility in which innovation can flourish in response to patients' needs." [27]

The South African Department of Health has also targeted the concept of establishing an "environment in which quality health care will flourish". *A Policy on Quality in Health Care for South Africa* suggests four methods to enable the establishment of such an environment: [28]

i. "Strengthening the hand of the user": empowering the patient population with the necessary information to make the correct decision on their health care
ii. "Focusing on equity of health care and vulnerable populations": to address the disparities in health resources and quality of care between different individuals and communities
iii. "Promoting public/private partnerships and the accountability of both sectors for quality improvement": a coordinated effort is required to improve quality of care, whereby the views and expertise of stakeholders in both sectors should be incorporated
iv. "Reducing errors and increasing safety in health care": an adverse events reporting system will help to enable system changes.

The report suggests steps to build the capacity to improve quality. These steps include: fostering evidence-based practice and innovation, adapting organisations for change; engaging the "health care workforce"; providing the necessary training and building the information systems' capacity to measure quality improvements.

Page 21 of the report explains the role of clinical audit: [28]

"Clinical audit is essential in patient care as it brings together professionals from all divisions of health care to:

i. Consider clinical evidence (evidence-based health care);
ii. Promote education and research;
iii. Develop and implement clinical guidelines;
iv. Enhance information management skills
v. Contribute towards better management of resources."

Importantly, this report makes it clear that, "All health professionals at all levels of care will participate in clinical audit." [28]

The tasks of clinical audit teams include:

i. "Determine what aspects of current work are to be considered for auditing;
ii. Describe and measure present performance and trends;
iii. Develop standards, if these are not available;
iv. Decide what needs to be changed;
v. Negotiate change;
vi. Mobilise resources to effect change; and
vii. Review and renew processes."

The report describes the ethos in which quality improvement may flourish: "a standardised managerial model will be developed to prevent the clinical audit and peer review process developing into a search for error only, which could lead to the denigration and condemnation of others." [28] It should not be a witch-hunt, but the emphasis should be on joining efforts for the common goal of improving the standard of care, and embracing the organisation's learning curve.

This idea is supported in a presentation by prof JV van der Merwe, Medical Advisor to Council for Medical Schemes, South Africa:

"For CLINICAL GOVERNANCE to be successful, health organisations must demonstrate the following features:

i. An open and participative culture
ii. A commitment to quality that is shared by staff and managers
iii. A comprehensive programme of quality improvement systems" [29]

The foreword of *Principles for Best Practice in Clinical Audit* (published by National Institute of Clinical Excellence, UK), provides an eloquent summary of the pivotal role of the medical audit:

"Clinical audit is at the heart of clinical governance.

i. It provides the mechanisms for reviewing the quality of everyday care provided to patients with common conditions like asthma or diabetes.
ii. It builds on a long history of doctors, nurses and other healthcare professionals reviewing case notes and seeking ways to serve their patients better.
iii. It addresses quality issues systematically and explicitly, providing reliable information.
iv. It can confirm the quality of clinical services and highlight the need for improvement." [25]

2.3 Literature Review: Medical Audit of Cryptococcal Meningitis Management

The researcher conducted a search on internet-based search engines: Google, Google Scholar and PubMed (http://www.ncbi.nlm.nih.gov/) and found a limited number of publications with the search terms of "Cryptococcosis", "Cryptococcal Meningitis", "audit" and "quality improvement".

2.3.1 An online PowerPoint presentation (on the website of the Department of Family Medicine of the Pietermaritzburg and Midlands Complex, South Africa) discussed the process of quality improvement and presented the findings of a CM audit at Northdale hospital, a district hospital in Pietermaritzburg, uMgungundlovu health district, KwaZulu-Natal, South Africa. [30] This hospital serves a population of about 200 000. [31] The motivation for this audit was recurrent readmissions for CM and varying length of stays and patient outcomes. The audit team consisted of the Clinical Head in the Family Medicine department, the Principal Family Physician, the Chief Family Physician, the Laboratory Microbiologist, the Principal Specialist in Infectious diseases, the Infection Control Practitioner and the Medical Ward unit manager. The audit team reviewed the clinical team's current practice of eighteen CM cases that were diagnosed during July 2006 at Northdale hospital.

The key findings were a follows:

i. Problems faced regarding managing CM-associated raised intracranial pressure (ICP): not measuring CSF opening pressures, no available spinal manometers, not recognising headache caused by raised ICP.

ii. Problems faced regarding general CM management: uncertainty regarding management protocol and when to discharge, failure to educate patients and family, uncertainty regarding management of CM re-admissions (especially regarding the need to repeat a diagnostic lumbar puncture).

iii. Problems faced regarding follow-up at Anti-Retroviral Treatment clinics and long-term Fluconazole management and adherence.

The key recommendations were as follows:

i. Addressing resource needs (manometers)

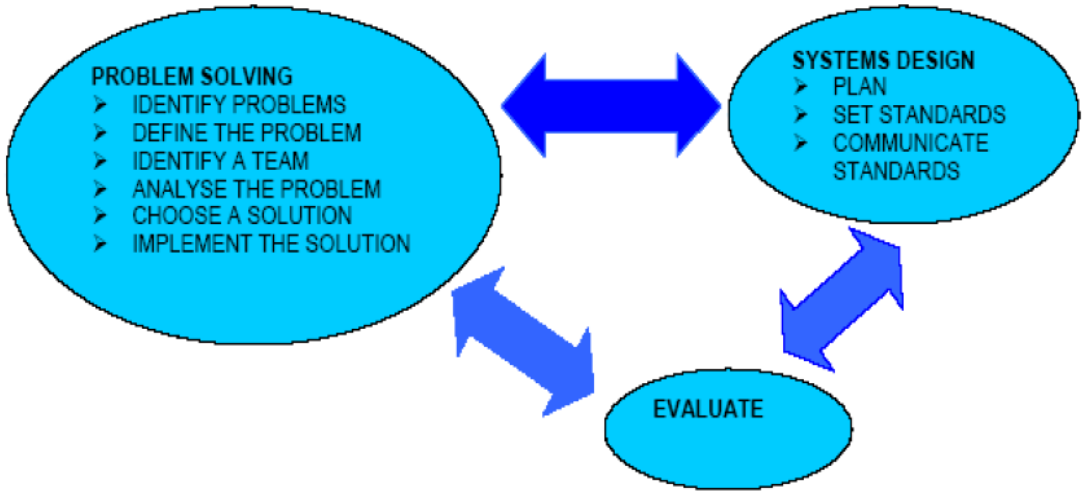
ii. Importance of ART clinic and CM management partnership

iii. Importance of diagnosing and treating raised ICP

iv. Addressing the need to develop a local CM treatment guideline

The presenter highlighted the Framework for the Quality Improvement Process (Figure 4) [30]

Figure 4 FRAMEWORK FOR QUALITY IMPROVEMENT PROCESS



2.3.2 In a report (2005) from two hospitals in Washington, DC, United States of America (USA), researchers emphasised the importance of adherence to guidelines for CM management. [32] The Infectious Diseases Society of America (IDSA) published these guidelines in 2000. [33] Although the terms "clinical/medical audit" or "quality improvement" were not used in this report, it could be seen as the first step of a quality improvement process: reviewing current practice against evidence-based guidelines. This study sought to assess the level of adherence with the guidelines and to describe the impact that deviation from these recommendations may have on clinical outcomes.

The researchers conducted a retrospective review of thirty-nine consecutive patients with cases of culture-proven, community-acquired meningitis. Twenty-six (67%) of these patients were diagnosed with CM. Cerebrospinal fluid opening pressure had been measured in thirteen (50%) of these twenty-six patients, and "major deviations from the

guidelines" with respect to raised ICP management were observed in fourteen patients (54%). "Major deviations" were defined as failure to measure the opening pressure with the initial lumbar puncture and/or failure to attempt to lower the ICP within 72 hours after the CSF pressure was measured to be more than 35 cm H_2O. Seven (50%) of these fourteen patients developed "neuropathies" (new or worsening cranial nerve deficit, confusion, hallucinations, or obtundation) during therapy, compared with one of the five patients whose care had minor or no deviations from the guidelines.

2.3.3 International examples of general QI projects in the HIV arena include:

2.3.3.1 HIVQUAL (HIV Quality of Care) is a United States of America (USA) model for building capacity for quality management that was designed to improve care for people living with HIV. [34] Originally, the New York State Department of Health AIDS Institute (NYSDOH AI) in partnership with the HIV/AIDS Bureau of the USA Health Resources and Services Administration (HRSA) developed this model. The National Project was launched in 1995 and has now expanded to over 200 sites in the USA.

This model consists of three key elements:

i. Quality improvement
ii. Performance measurement
iii. Infrastructure and capacity building

HIVQUAL International (HIVQUAL-I), modelled after the New York programme (HIVQUAL), was started in 2003 in Thailand, and has since expanded to Uganda, Mozambique, Namibia, Nigeria, Haiti, Guyana, Kenya, Botswana, Rwanda, Vietnam and Swaziland. The HIVQUAL model has been successfully adapted in these countries, adjusting for differences in guidelines, resources and healthcare models. Central to the HIVQUAL approach to quality management is the emphasis on the development of systems and processes to support quality improvement activities, which involve clinic staff and patients, with support from HIVQUAL programme leadership. Structural features are designed to be sustainable. HIVQUAL-I is supported by the Office of the Global AIDS Coordinator (OGAC), the Centre for Disease Control (CDC) Global AIDS

Programme (GAP) Office in each country, where the project is integrated into the national AIDS programme.

HIVQUAL-I is also supported through HRSA as the International Quality Center for USA President's Emergency Plan for AIDS Relief (PEPFAR) and through funding from United Nations Children's Fund (UNICEF).

2.3.3.2 Thailand's programme, HIVQUAL-T, aims to develop a comprehensive HIV care model in Northern Thailand. Several governmental and non-governmental partners are involved in this Quality Improvement process. A dedicated QI budget, nation policy, consultant-led audit teams and group-learning meetings support this system. [35]

2.3.3.3 In the USA, the New York Department of Health AIDS Institute's (NYSDOH AI) National Quality Center, in partnership with the Health Resources and Services Administration's (HRSA) HIV/AIDS Bureau (HAB) developed a comprehensive guide (2008): *Guideline-based Quality Indicators for HIV Care*. [36] This guide contains performance measures that "represent not just what constitutes good medical therapeutics, but also reflect the comprehensive package of services that is critical for providing the best possible care to patients with HIV".

A panel of clinical experts developed this quality improvement resource, which provides eleven sets of HIV-specific performance measures. The measures can be adapted by HIV programmes and contribute to providing the highest standards of care to HIV-infected patients. These indicators are categorised within the following aspects of HIV care and treatment: HIV primary care, perinatal care, tuberculosis, sexually transmitted diseases (STD), hepatitis, prevention, mental health, substance use, occupational post-exposure and oral health. Performance measures for opportunistic infections are also included.

These performance measures are aimed at busy health care workers and provide access to evidence-based HIV-specific indicators. Each measure is described by citing relevant guidelines, scientific background information and detailed indicator definitions. These indicators allow health care workers to measure the quality of the care provided. The performance data should then be used to improve key aspects of HIV care (implement change).

The measures for CM are provided in the format used throughout the document:

i. *"Eligible Population*: All HIV-infected patients

ii. *Denominator Description*: Number of HIV-infected patients with cryptococcal meningitis

iii. *Numerator Description*: Number of patients with cryptococcal meningitis who received therapy with at least 2 weeks of an amphotericin B preparation, followed by at least 22 weeks of fluconazole." [36]

Reporting of these indicators is not required, nor is national reporting systems for these indicators in place. This differs from the HIVQUAL indicators, that are reviewed annually and revised accordingly, and are the standardised measures for reporting the quality of HIV care by HIV ambulatory care programmes participating in the USA HIVQUAL programme.

In summary, the topic of Quality Improvement is not new to the HIV context. However, a search of the published literature showed a limited number of CM specific medical audits. It is important to focus on the quality of comprehensive care, but the value of quality management of specific opportunistic infections (such as CM) needs emphasis.

3. Aim and Objectives

3.1 Aim: This medical audit aimed to improve the quality of the clinical care of Human Immunodeficiency Virus (HIV)-patients diagnosed with Cryptococcal Meningitis (CM) in the Cape Winelands (East) district by evaluating the clinical team's awareness of and adherence to national treatment guidelines following the interventions proposed by the findings of the pilot audit.

3.2 The Objectives of the audit on the quality of care for CM in Level 1 and 2 hospitals were:

a. To review existing and create new appropriate target standards for the management aspects of CM
b. To demonstrate an improvement in the quality of CM care at the Level 2 hospital, considering the effect of the intervention after the pilot audit
c. To identify strengths and weaknesses in the quality of CM care at Level 1 and Level 2 hospitals
d. To reflect on the quality of CM care at Level 1 compared to Level 2 hospitals
e. To identify key interventions that may improve the quality of care of CM patients
f. To provide recommendations to the facilities and department of health

4. Methods

4.1 Study Design Choice and Rationale:

Medical/Clinical Audit (Quality Improvement cycle). Audit is about monitoring performance against established standards, and implementing appropriate change, as necessary, to meet these standards. Continuous Quality Improvement is an important aspect of the process of clinical governance: it involves both the critical application of research evidence and the formal evaluation of that application in the form of an audit.

The initial pilot audit in 2008 (the Worcester hospital experience) revealed that certain important target standards have not been met. The findings provided sufficient motivation to continue the audit cycle. A list of recommendations was compiled and these were used to educate the health care team (implementation of the intervention), before the researcher and the audit team commenced the subsequent audit cycle in the larger geographical area: the eastern part of the Cape Winelands district (Brewelskloof, Ceres, Montagu, Robertson and Worcester hospitals).

There are advantages to involve the district hospitals in the Cape Winelands (East) district in the audit: larger study population; reaching and educating a larger number of health professionals about the latest national guidelines; identifying issues unique to managing CM in the district hospital setting.

4.2 Evidence base

The guidelines for the management of CM (for the purpose of this audit) are those published in the Spring 2007 edition of *The South African Journal of HIV Medicine* (Official Journal of the South African HIV Clinician Society): *Guidelines for the Prevention, Diagnosis and Management of Cryptococcal Meningitis and Disseminated Cryptococcosis in HIV-infected patients.* [19]

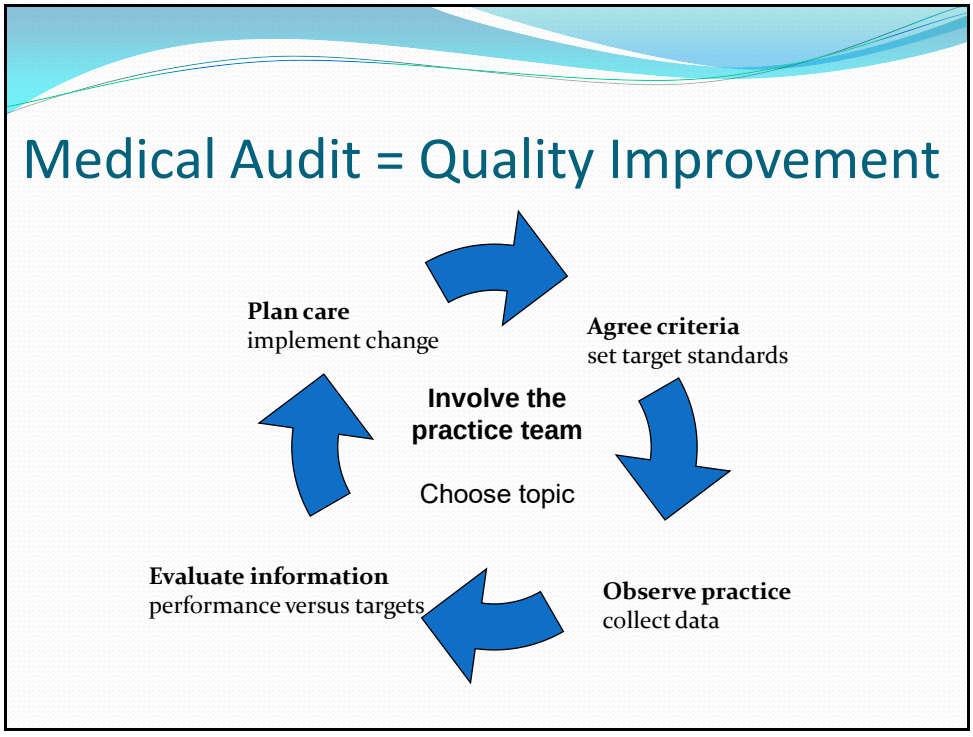
4.3 Timeframe of Audit

The timeframe consisted of five phases:

i. Team formation and setting of new criteria: September and October 2009
ii. Implementation of changes to improve the quality of care: September and October 2009
iii. Collect data: November 2009 – June 2010
iv. Analysis of data: July – August 2010
v. Reflection and planning of new changes: July – August 2010

4.4 The method reflects the steps of the audit cycle, starting with the intervention following the pilot audit:

Figure 5: Copy of PowerPoint Slide used in Teaching Intervention: the Quality Improvement Cycle



4.4.1 Step 1: Intervention: plan changes based on findings of the previous pilot audit

The main intervention based on the findings of the pilot audit was the education of the health professional team treating CM patients at the hospitals in this district. The team was educated on the correct treatment of CM (based on the national guidelines compiled by the SA HIV Clinician Society in 2007). [19]

Teaching activities formed the basis of the educational intervention. During September and October 2009, the researcher arranged a meeting at each hospital involved in the audit. Figure 5 shows a slide from the PowerPoint presentation used.

A one hour-long interactive teaching session was held at Worcester hospital on 30 October 2009. All health care personnel of the departments of Internal Medicine, Family Medicine and the ART clinic were invited. Fifteen people (including the researcher) attended the session. The crossover/jigsaw small group technique was used which involves two phases:

Phase 1: Four Expert Groups (each with a facilitator) discussed the following topics:

- A: LP and Spinal Manometry
- B: Amphotericin B use and pre-cautions
- C: Medical Audit practicalities (including review of criteria and target standards)
- D: ART work-up and follow-up

During Phase 2, a member of each Expert Group reconvened to form a Home Group: each person had to present a summary of the discussion in the individual Expert Groups. This technique promotes active participation and learning.

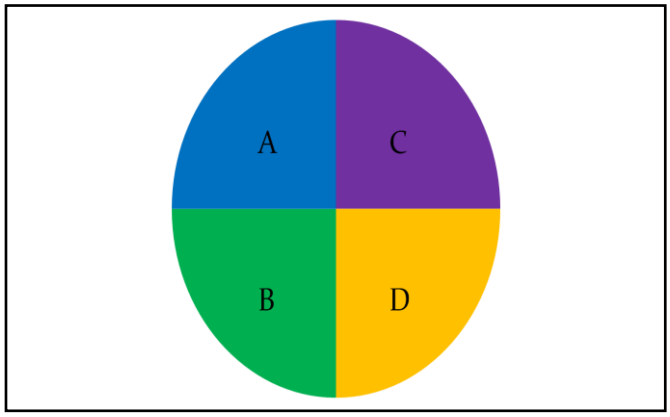


Figure 6: The Home Group

The One Minute Paper (a classroom assessment technique) was used to obtain feedback from the group. One open question was asked: "Regarding the management of Cryptococcus Meningitis patients: which aspect of your management of these patients will change after today's discussion?" Addendum 2 shows the feedback from the attendees.

Similar educational sessions were conducted at the other hospitals involved in the audit.

These teaching activities had two main goals: to introduce the planned audit (and the concept of improving QOC via an audit) and to recruit members for the audit team; and, to familiarise the team with the CM treatment guidelines. The educational presentation focused on the problem areas identified by the pilot audit, specifically: the correct administration of Amphotericin B, the appropriate use of spinal manometry and the need for fast-tracking ART counselling and initiation. The importance of adhering to the national treatment guidelines during the first two weeks of management was emphasised. This "A2A" (Ampho B to ART) period may have the greatest impact on the mortality associated with CM.

Structural interventions entailed ordering and stocking of spinal manometers (by involving the hospital management). The researcher distributed posters and handouts describing the CM treatment guidelines (see Addenda 3, 4 and 5: these documents were part of the standard set of audit documents, including a poster and printed guidelines, that was distributed by the researcher at each hospital involved in the audit). The poster (Addendum 6) was included in the Spring 2007 edition of the *The South African Journal of HIV Medicine.* [19] The researcher obtained permission from the publisher to replicate the posters for distribution in the hospitals.

Furthermore, the researcher and the audit team liaised with the ART clinics to ensure "fast-tracking" of the ART counselling and introduction process. The ART clinicians were invited onto the audit team.

4.4.2 Step 2: Create a new audit team

The clinical audit team of the Cape Winelands (East) sub-district consisted of the researcher, the Clinical Programme Coordinator: Infection Prevention and Control, as well as key individuals (audit champions) from the sub-districts, who represent their hospital's audit team. Involvement and cooperation of all relevant health care personnel (managers, doctors, nurses, pharmacists, laboratory technicians, ART clinic personnel) was recommended in order to ensure a successful audit process.

4.4.3 Step 3: Revise old and develop new criteria and target standards

The researcher involved the audit team to formulate the target standards for each criterion of the CM management process.

"The target standard of care is the result of a well-defined and measurable criterion, as well as a level of performance for that criterion." [38]

The criteria selected represent the three audit areas of *Structure, Process* and *Outcome*. Listed below are the criteria. The level of performance (target standard) for each criterion is provided in Table 1. The target standards for the initial pilot audit at Worcester hospital were developed in 2008. The researcher compiled the list of criteria after a thorough literature review and after discussion with both the Physician and the Family Physician at Worcester hospital.

The researcher and the audit team revised existing criteria and included new criteria prior to the new audit cycle. The new/modified criteria appear in **Bold** in Table 1.

In the pilot audit, *Adherence to long-term Fluconazole (secondary prophylaxis)* was included as a criterion. The researcher removed this criterion from the audit, as the criterion was difficult to measure due to paucity of post-discharge information (short period of follow-up). The HIV Clinician Society of South Africa recommends the following secondary prophylaxis regime (to prevent recurrences of CM): Fluconazole 200mg daily for life (or until CD4 > 200cells/µl for more than 6 months on ART, at least 12 months' Fluconazole in total). [19] (The Level of Performance for the criterion in the pilot audit was 80%, as patient, socio-economic, disease or health system-related factors could prohibit total adherence.)

Table 1 References: The source of evidence for each criterion's target standard is shown in the table.

The audit team reached consensus for two of the outcome criteria using the following two references (see Table 1: Criteria 3.3 and 3.4)

x. Drug information on Ampho B listed thrombophlebitis in the group of adverse events that are typically found in 10% (or more) of patients exposed to the drug. [39, 40]

y. An article from Uganda on the outcomes in CM management in the pre- and post-ART era mentioned Sub-Saharan mortality figures of up to 36%. [18] The researcher and audit team would like to see that six out of ten patients (60%) diagnosed with CM are still alive two months after diagnosis, as the same treatment protocol is used.

Table 1: Audit Criteria (New/modified criteria are highlighted in **Bold)**		**Target: Level of Performance**	**Source of Evidence**
1.Structure	*1.1 Availability of Amphotericin B* This drug should be available in the wards to avoid delay in starting fungicidal treatment of fourteen days	100%	Audit Team Consensus
	1.2 Availability of Fluconazole This drug should be available to continue with the consolidation phase after completion of the Amphotericin B course.	100%	Audit Team Consensus
	1.3 Protocol (Poster and treatment guidelines) for the administration of Amphotericin B in wards Nursing professionals and doctors should know how to prepare the Amphotericin B solution and how to administer it correctly. The researcher provided a set of posters and treatment guidelines to each hospital prior to commencement of the data collection period.	100%	SA HIV Clinician Society Guidelines and Audit Team Consensus
	1.4 Availability of Spinal Manometers Spinal Manometers should be available when performing Lumbar Punctures (LP's) on CM patients (availability may vary, as certain hospitals had to order manometers for the first time prior to this audit)	80%	SA HIV Clinician Society Guidelines
2.Process	*2.1 CT scan if depressed Level of Consciousness/Focal Neurology* In those patients with a depressed GCS (Glasgow Coma Scale < 15/15) or any focal neurological signs (i.e. where a LP would be contra-indicated), a CT scan of the brain should be requested.	100%	SA HIV Clinician Society Guidelines
	2.2 Use of CSF manometry in all initial LP's All patients who require a LP should have their initial CSF opening pressure measured. Early diagnosis of raised CSF pressure (>20 cmH_2O) would facilitate early therapeutic taps and improve outcome.	100%	SA HIV Clinician Society Guidelines

Table 1: **Audit Criteria (**New/modified criteria are highlighted in **Bold)**	**Target: Level of Performance**	**Source of Evidence**
2.3 Follow-up Manometry post-CM diagnosis when raised opening pressure (OP) with initial LP or symptoms of raised ICP In those patients diagnosed with CM, a follow-up manometry should be performed if an initial OP was raised or if the patient had symptoms of raised ICP. (Problems with availability of manometers may hamper this process. The researcher and audit team would like to see that the current practice reaches this target; the target may be changed to 100% for future practice.)	80%	SA HIV Clinician Society Guidelines
2.4 Requesting CLAT on Indian ink-negative CSF samples If the initial Indian ink stain (available at the local NHLS Laboratory in Worcester) on the CSF specimen is negative, a CLAT (*Cryptococcus Latex Antigen Test*) should be requested. This test is done at the National Health Laboratory Service (NHLS) Laboratory in Greenpoint, Cape Town (not available at the local NHLS Laboratory in Worcester).	100%	SA HIV Clinician Society Guidelines
2.5 Completing target of fourteen days of IV Amphotericin B The accepted duration of treatment for IV Amphotericin B in HIV-positive patients in fourteen days (two weeks) – this is the initial or induction phase of antifungal treatment where a fungicidal drug is used. (Level of Performance = 80% ; a minimum duration of treatment equals seven to ten days)	80%	SA HIV Clinician Society Guidelines
2.6 Using correct dose of Amphotericin B (1mg/kg) The accepted dose of Amphotericin B is 1mg/kg, when used without Flucytosine . Previously, a dose of 0,7mg/kg has been used widely. This dose was intended for use in combination with Flucytosine. However, Flucytosine is not currently available in South Africa.	100%	SA HIV Clinician Society Guidelines
2.7 Average number of U&E, Mg tests whilst on Amphotericin B (initial and two/week) During the standard fourteen-day Amphotericin B treatment period, an average of five U&E and Mg tests should be performed on each patient (one initial value and two tests per week, if no abnormal findings – with abnormal test results, the tests should be performed more often).	100%	SA HIV Clinician Society Guidelines and Audit Team Consensus

Table 1: Audit Criteria (New/modified criteria are highlighted in **Bold)**		**Target: Level of Performance**	**Source of Evidence**
	2.8 Saline preload prior to daily Amphotericin B dose A liter of normal saline (with one ampoule of 20 mmol KCl) should be administered daily prior to the daily Amphotericin B dose. This helps to prevent Amphotericin B associated renal impairment and hypokalaemia.	100%	SA HIV Clinician Society Guidelines
	2.9 Saline IV flush after daily Amphotericin B dose The IV access of each patient should be flushed with normal saline after completion of the daily Amphotericin B dose. This simple procedure reduces the risk of Amphotericin B associated thrombophlebitis.	100%	SA HIV Clinician Society Guidelines
	2.10 Referral for inpatient ART counselling "the long in-hospital stay associated with Amphotericin B therapy should facilitate pre-ART counselling, identification of a treatment supporter and early referral to an ART centre". [19]	80%	SA HIV Clinician Society Guidelines
	2.11 High dose Fluconazole for eight weeks (consolidation phase) The accepted duration of the consolidation phase is eight weeks, where the fungistatic drug, Fluconazole is used at the dose of 400mg daily.	100%	SA HIV Clinician Society Guidelines
	2.12 Referral to ART clinic CM is an AIDS-defining disease and referral for ART treatment is indicated.	100%	SA HIV Clinician Society Guidelines
3.Outcome	*3.1 Commencement of ART by week four into antifungal treatment* "Evidence for the optimal timing of ART initiation is not available: we believe ART is most appropriately started 2 – 4 weeks after treatment for [cryptococcosis] has commenced. Although no prospective evidence exists in this regard, given these patients' advanced immunosuppression, delaying ART introduction beyond 4 weeks to reduce the risk of IRIS may increase the risk of mortality." [19]	80%	SA HIV Clinician Society Guidelines and Audit Team Consensus

Table 1: Audit Criteria (New/modified criteria are highlighted in **Bold)**		**Target: Level of Performance**	**Source of Evidence**
	3.2 Morbidity: incidence of Amphotericin B associated renal impairment Major side-effects of Amphotericin B include renal impairment due to renal tubular toxicity (usually in the second week of therapy). The SA Journal of HIV Medicine[1]: "Nephrotoxicity and electrolyte abnormalities may be prevented by prehydration with normal saline containing potassium. Nephrotoxicity usually occurs in the second week of therapy with amphotericin B; baseline and twice-weekly monitoring of creatinine, potassium and magnesium is appropriate. If creatinine doubles, consider omitting a dose of amphotericin B or increasing prehydration to 1 litre 8- hourly. If creatinine remains elevated, stop amphotericin and use fluconazole." [19] (Level of Performance = 20% = the audit team would like to see that only one in 5 patients suffer from this potentially preventable complication)	20%	SA HIV Clinician Society Guidelines
	3.3 Morbidity: Amphotericin B associated thrombophlebitis The risk of Amphotericin B associated thrombophlebitis is reduced by flushing the IV access of each patient with normal saline after completion of the daily Amphotericin B dose. (Level of Performance = 10% = the audit team would like to see that only one in 10 patients suffer from this potentially preventable complication)	10%	Audit Team Consensus, based on evidence [x]
	3.4 Two-month-survival post-diagnosis The researcher wants to know the percentage of living patients two months after the initial diagnosis of CM was made. It should be comparable to Sub-Saharan and/or National Standards. [18, 41] (Level of Performance = 60% = the researcher and audit team would like to see that 6 out of 10 patients diagnosed with CM are still alive two months after their diagnosis has been made. The Sub-Saharan figures mentioned, show that the mortality is up to 36%; therefore, the survival should be at least 60% in the Cape Winelands (East) setting, as the same treatment protocol is used.)	60%	Audit Team Consensus, based on evidence [y]

4.4.4 Step 4: Collection of data to measure these target standards

4.4.4.1 Study population: All adult (>13 years) HIV-positive patients diagnosed with Cryptococcal Meningitis (CM) and treated at the hospitals in the eastern part of the Cape Winelands District, were included into the audit. Only those patients diagnosed with CM in the specified period (November 2009 to June 2010) were enrolled.

Patients with CM were diagnosed when the CSF tests for CM were positive (Indian ink test or CLAT). A CLAT titer of equal or greater than 1:8 was considered positive and a titer less than 1:8 was considered negative (this was agreed on in conjunction with the clinical microbiologist at Greenpoint NHLS laboratory, where the CLAT tests were done, after consultation with the package insert of the CLAT test in use).

The treatment guidelines for HIV-positive and HIV-negative patients differ substantially. CM is a rare diagnosis in HIV-negative patients (typically, there is another source of immune suppression, as CM is an opportunistic infection). Only HIV-positive patients were included in the audit.

4.4.4.2 Data source: A prospective data collection process was planned: the team would start to collect the data on diagnosis and continue during the period of care, but the data analysis would start only after the completion of the data-capturing period.

This data collection plan included a confidential data-capturing sheet, that was to be completed on admission (see data capturing sheet in Addendum 3) and kept up to date during the pre-determined follow-up period (admission, inpatient stay, discharge, ART clinic follow-up). The audit team had to notify the researcher (audit lead) of every patient on discharge (a unique CMA number was supplied to each case, in order to ensure confidentiality). The researcher kept the list of cases with their respective identifiable data in a secure place.

The researcher and the audit team experienced practical difficulties with the planned prospective data collection process. The Level 1 hospitals were adherent to the data collection procedure, but the researcher received no completed data capturing forms from the Level 2 hospital. The researcher contacted senior members of the Level 2 hospital's clinical team to remind them of the audit during the data collection period.

To address case underreporting due to non-adherence to the data collection method, the researcher arranged with the National Health Laboratory Service (NHLS) laboratory to obtain a list of all CM-related tests from November 2009 until June 2010.

After using the official application process, the NHLS laboratory sent the researcher an Excel Pivot Table with a list of patient folder numbers of all Cryptococcus-related tests requested during the period of November 2009 until June 2010 at the hospitals included in the audit. The only identifiable patient details were the patient folder numbers. These were used in a confidential manner. This NHLS-generated list identified 55 patients with positive CM-related tests (including those with a CLAT titer < 1:8).

The following criteria determined the audit study population. All cases that met the criteria were included in the audit. No sampling was done.

4.4.4.3 CM Audit Inclusion criteria:

- HIV positive
- Adult (age > thirteen years)
- CM (CLAT and/or Indian ink positive; CLAT titer ≥ 1:8 on CSF)
- Hospital clinical records available
- Admission to a hospital of the Cape Winelands (East) district and/or diagnosis of CM at a hospital of the Cape Winelands (East) district
- Diagnosis or admission during the following period: 1 November 2009 to 30 June 2010

4.4.4.4 CM Audit Exclusion criteria:

- HIV negative
- Child (age ≤ thirteen years)
- No CM (Indian ink and CLAT negative; CLAT titer < 1:8 on CSF)
- Hospital clinical records unavailable

4.4.5 Step 5: Analysis of the data and compare results to target standards

The researcher consulted Prof M Kidd, from Stellenbosch University's Centre for Statistical Consultation (CSC), who has explained that clinical relevance (as opposed to statistical significance) is much more important in the audit setting. Chapter 13 (Medical audit and clinical governance) of the book, *Research Methods and Audit for General Practice* supports this principle: clinical relevance is the main goal of an audit. [42]

Addendum 7 shows the data presentation format (the results of the 2008 pilot audit at Worcester hospital).

Data from the audit was analysed and compared to the target standards. MS Excel was used to present the data in graphs.

The researcher has also reviewed the available folders regarding ART management at Worcester hospitals' infectious diseases clinic (integrated TB and HIV management).

The cut-off date for admission of data for analysis was 9 July 2010. After this date, no new data was collected for analysis.

Step 6 of the audit cycle (providing feedback to the clinical team and implement change) does not form part of the methods for this thesis. It will be discussed in the recommendations section.

4.5 Ethical considerations and Human Research Ethics Committee (HREC) approval

As stated in the South African Department of Health's Ethical Guidelines, the main consideration should be to conduct this clinical/medical audit in such a manner that the autonomy and dignity of patients with CM is respected. [37] This medical audit was ethically relevant to the patients and health professionals in the Cape Winelands (East) district, as this will provide a cyclical review process to improve the quality of care received by CM patients.

Patients with AIDS and CM represent a vulnerable group of individuals. The researcher and the audit team were fully aware of this fact. Proper respect for the patient's autonomy by obtaining informed consent prior to inclusion into the audit was a challenging situation. Informed consent implies that the patient should have full mental capacity as an adult. In some patients with CM, informed consent was not feasible: CM implies that the central neurological system is infected, which may result in impairment of higher functions and consciousness level. Furthermore, as this was an audit process that reviewed the effects of implementing clinical guidelines based on international evidenced-based recommendations, these patients received only the recommended standard medical treatment. No placebo or alternative management options were considered. Patients were included and excluded into the audit based on unbiased clinical criteria. Each case received a unique CM Audit number in the data capturing sheets. This ensured complete confidentiality and personal data protection.

Therefore, the researcher applied to the ethics committee for a waiver of informed consent. There was no disadvantage to the patients or their relatives that would compromise their rights and dignity to an extent unreasonable and unjustified in terms of the benefits of the medical audit.
Hospital Managers/Superintendents and the Director of the Cape Winelands Health District gave their custodian consent for the audit. The study protocol (research proposal 2010 RP 89) has been approved by the District Health Services and Health Programmes, Provincial Government of the Western Cape.

The Health Research Ethics Committee (HREC) of the Faculty of Health Sciences, Stellenbosch University, approved the study protocol on 8 December 2009 (Ethics Reference no: N09/08/205). (See Addendum 1: Letter of Approval from HREC committee)

5. Results:Cryptococcal Meningitis (CM) Audit: Cape Winelands (East) District

The data is presented in the following sequence: demography, analysis of management process and comparison of level of performance.

Demography of Study Population

5.1 Study Population

5.2 Demographics of patient study population (all patients, as well as individual hospitals)

Analysis of Cryptococcus Meningitis Management Process

5.3 Spinal Manometry Data

5.4 Amphotericin B Data

5.5 Data on Patient Deaths

5.6 Renal monitoring whilst on Amphotericin B

5.7 ART referral Data

Comparison of Level of Performance

5.8 Comparison of Level of Performance to Target standard (total patient study population)

5.9 Comparison of Level of Performance: Level 1 vs. Level 2 hospitals

5.10 Comparison of Level of Performance: Worcester Regional Hospital: Pilot Audit (2008) vs. Re-Audit (2010)

5.1 Study Population

Based on the inclusion and exclusion criteria the following patient folders were excluded.

Table 2: Original NHLS-generated list of patient folder numbers (NHLS = National Health Laboratory Service)		**55**
Exclusion:	HIV (Human Immunodeficiency Virus) negative status of patient	5
	False Positive CLAT (Cryptococcal Latex Agglutination Test) test (according to clinical records) on CSF (Cerebrospinal Fluid)	4
	Negative CLAT test (CLAT titer < 1:8) on CSF	3
	Cryptococcal culture positive on Pleural Fluid (not CSF)	1
	Age ≤ thirteen years (all had CLAT titer < 1:8)	6
	Discharged prior to CLAT result available, lost to follow-up (not admitted for inpatient care)	3
	Patient self-discharged (refused hospital treatment)	1
	Hospital clinical records not available	2
	Duplication of folder numbers (patients had a CLAT test at one hospital, but were transferred to a different hospital within the same district for further inpatient care)	3
	Patient transferred to another hospital within **another** district for further inpatient care	2
New Total: Patient folders included in this audit (N = study population)		**N = 25**

It is important to note that Montagu Hospital had no CM patients as inpatients during the data collection period.

Furthermore, N (total number of cases identified as the representative study population for inclusion in the medical audit) fluctuates. The number of cases was less in certain sub-sections of the results analysis (for example, the number of patients exposed to Ampho B is less than N).

5.2 Demographics of total patient study population

Twenty-five patient folders were included in the study population. The CD4 (Cluster of Differentiation 4) count is provided as cells per µL (microliter) or mm^3 (cubic millimeter). Three patients had documented previous episodes of CM. All three cases where treated with Amphotericin B. Management of suspected CM IRIS (Immune Reconstitution Inflammatory Syndrome) was not evaluated in this audit. Twenty percent of the study population was already on Anti-Retroviral Therapy (ART) at the time of CM diagnosis.

Table 3a: Demographics of the total study population

ALL PATIENTS	***Male***	***Female***	***Total***
Number of Patients in Audit	**13**	**12**	**25**
Average Age (years)	40	33	37
Average CD4 count at CM diagnosis	131	82	108
Average inpatient stay, if available (in days), for those patients that were discharged	40	28	34
Number of Patients with previous diagnosis of CM	2	1	3
Number of Patients already on ART at CM diagnosis	3	2	5

The demographic data from each hospital is presented in Table 3b.

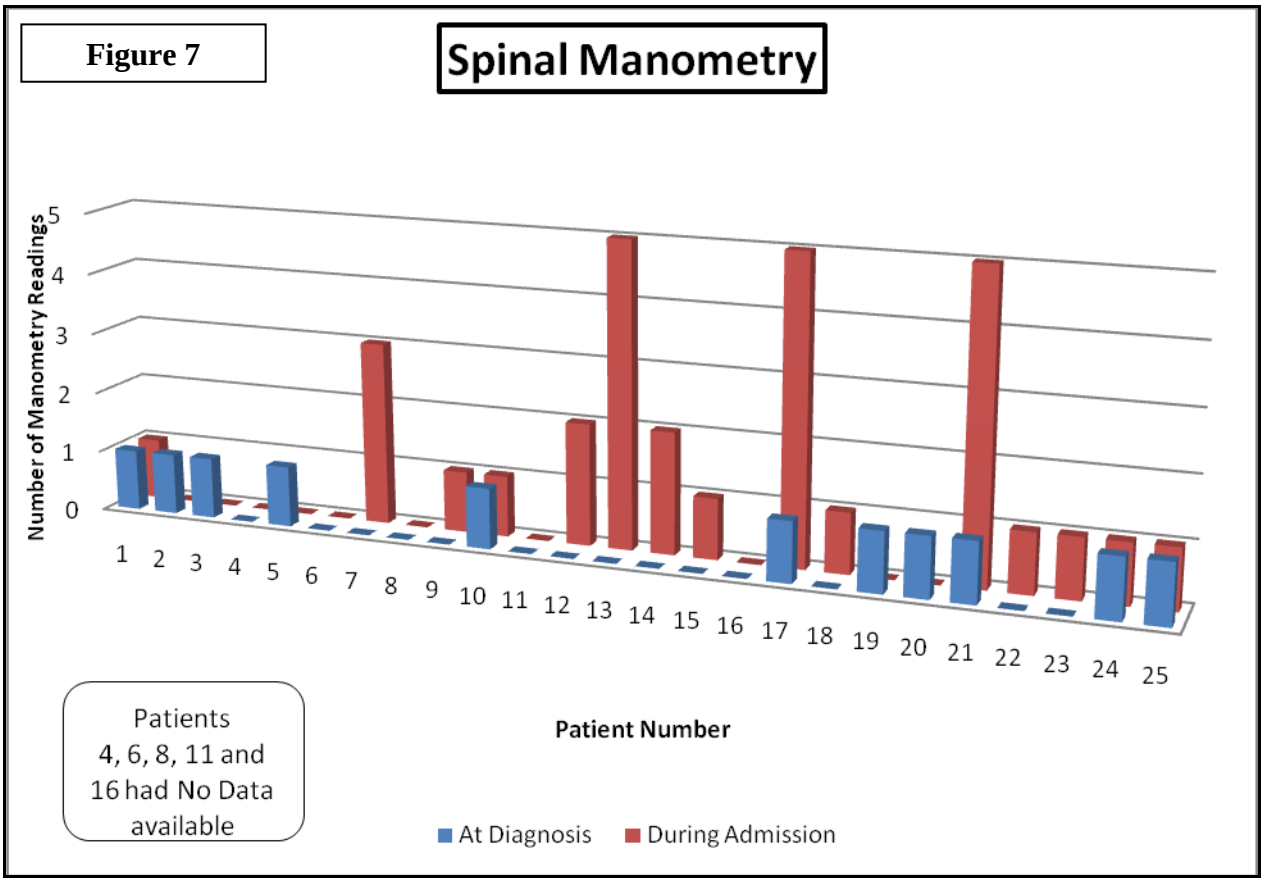
Table 3b: Demographics of the total study population (per hospital)

PER HOSPITAL	***BH***	***CH***	***RH***	***WH***	***Total***
Number of Patients in Audit	**5**	**3**	**3**	**14**	**25**
Average Age (years)	39	32	46	35	37
Average CD4 count at CM diagnosis	113	121	89	108	108
Average inpatient stay, if available (in days), for those patients that were discharged	84	24	16	26	34
Number of Patients with previous diagnosis of CM	1	1	1	0	3
Number of Patients already on ART at CM diagnosis	3	1	1	0	5

The average inpatient stay in Brewelskloof hospital (BH), a specialised tuberculosis hospital, is expected to be above average, as these cases are admitted for inpatient tuberculosis management in sub-acute beds. Due to the increased incidence of HIV and tuberculosis co-infection, opportunistic infections (such as CM) occur in the BH patients.

5.3 Spinal Manometry Data (Figure 7 and Table 4)

Data regarding the process of spinal manometry is presented in figure 7. Patients 4, 6, 8, 11 and 16 had no recorded data in the clinical notes regarding this management criterion (20 % of the study population).



Eleven patients (44 % of the study population) had spinal manometry with the initial (diagnostic) lumbar puncture (LP). 95% had a raised intracranial pressure (ICP) reading with any LP during the inpatient treatment period. Ten of the eleven patients with initial spinal manometry readings had opening pressures greater than 20 cmH_2O (raised ICP). Patient 21 had an initial opening pressure of 15 cmH2O (ICP not raised), but required five further manometry measurements during the admission period.

Table 4: Spinal Manometry	N = 25 (100 %)
1. Spinal manometry at diagnosis (with initial LP)	11/25 patients = 44 %
2. Patients who had at least one measurement during inpatient stay	20/25 patients = 80 %
3. All patients with manometry measurements, who had at least one elevated reading (equal or greater than 20 cmH_20)	19/20 patients = 95 %
4. No documented measurements found in clinical records	5/25 patients = 20 %

5.4 Amphotericin B Data (Table 5 a-b, Figure 8)

Five patients (20%) of the study population were not exposed to Amphotericin B (Ampho B) treatment. Of the remaining twenty patients, 9 patients (45 %) managed to reach the target of fourteen days on Ampho B. An unexpected finding was the interruption of treatment due to no Ampho B stock. Three patients (15 %) had their Ampho B treatment interrupted due to Ampho B associated renal toxicity.

Table 5: Amphotericin B Data

a. Patient data eligible for analysis of Ampho B treatment process	Total	Breakdown
Total Patient Files / Clinical records	**25**	
Exclusion (non-exposure to Ampho B or current inpatient)	**5**	
Inpatient Death prior to start of Ampho B		3
Prior renal impairment (Ampho B contra-indicated)		1
Exclusion : Current inpatient status (Ampho B in progress)		1
Inclusion (exposure to Ampho B)	**20**	
Completion of 14 day Ampho B course		9
Interruption due to Inpatient Death whilst on Ampho B		3
Interruption due to No Ampho B Stock		5
Interruption due to Ampho B related renal impairment		3

Patient 17 was an inpatient at the time of data analysis.

b. Reasons for Patients who did not reach the 14 days course Amphotericin B target:	**Number of patients**
No Amphotericin B stock available	*5*
Death as inpatient *see separate table (below)	3
Ampho B associated renal impairment	3
Total	**11**

Table 5b's data (Reasons for not reaching the 14 day Ampho B target) is displayed in the pie chart below (Figure 8).

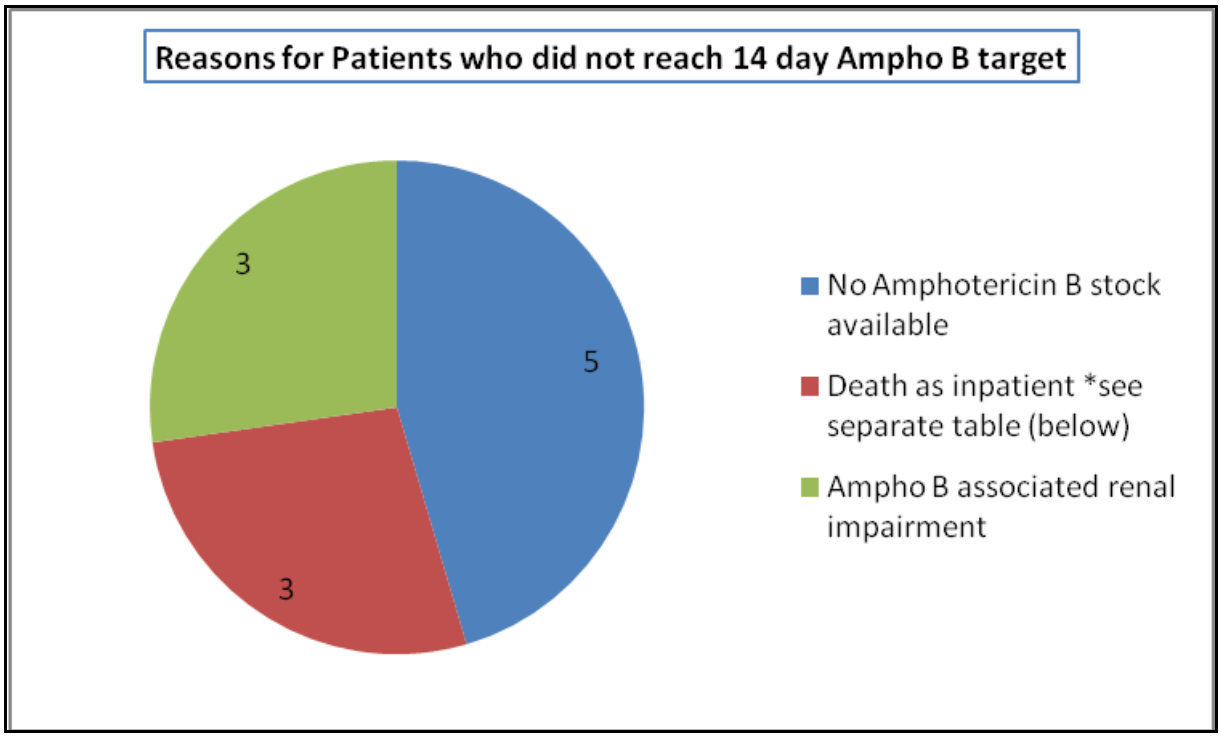


Figure 8

*Refer to Table 6

5.5 Data on Patient Deaths

Table 6 looks at patients' death in the context of Amphotericin B (Ampho B) treatment, which represents the main component of inpatient medical treatment. The middle column of table 6 describes those patients who did not complete the Ampho B due to inpatient death.

Table 6: Patients who *died* prior, during and post-Amphotericin B

Died ***as inpatient prior*** *to start of Ampho B course* *(Reason for delay to treatment in brackets)*	*Died* ***as inpatient during*** *Ampho B course* *(Duration of Ampho B treatment in brackets)*	*Died* ***after*** *completion of Ampho B* *(Duration between end of Ampho B course and patient death in brackets)*
Patient 11 *(Diagnosis of CM and patient death on the same day)*	Patient 2 *(1 day)* *(Did not complete course due to death)*	Patient 8 (Died post-discharge from hospital) *Patient died 4 months after discharge from hospital; co-infection with disseminated tuberculosis; not on ART at time of death)*
Patient 18 *(Died the evening after having been admitted for Ampho B treatment: convulsion and focal neurology preceded death)*	Patient 22 *(4 days)* *(Did not complete course due to death)*	Patient 14 (Died as inpatient) *(Died 10 days after completion of Ampho B due to chest infection and bicytopenia; not on ART at time of death)*

Table 6: Patients who *died* prior, during and post-Amphotericin B		
*Died **as inpatient prior** to start of Ampho B course* *(Reason for delay to treatment in brackets)*	*Died **as inpatient during** Ampho B course* *(Duration of Ampho B treatment in brackets)*	*Died **after** completion of Ampho B* *(Duration between end of Ampho B course and patient death in brackets)*
Patient 20 *(Died 1 day after positive CLAT result: Ampho B prescribed but patient died before receiving 1st dose)*	Patient 25 *(1 day)* *(Did not complete course due to death)*	Patient 21 (Died as inpatient) *(Died 4 days after completion of Ampho B; cause of death unclear from clinical notes; not on ART at time of death)*
	Patient 7 *(8 days)* **Ampho B treatment was interrupted due to no Ampho B stock**; the patient died two days later as inpatient.	Patient 23 (Died as inpatient) *(Died 1 day after completion of Ampho B; cause of death unclear from clinical notes; not on ART at time of death)*
3	**4**	**4**

Patient not included in this table (not treated with Amphotericin B): Patient 4 was not started on Ampho B due to previous renal impairment (Ampho B was contra-indicated).

In summary, twelve patients (48% of the study population) died and eleven patients (44%) did not reach the two-month post-diagnosis target (patient 8 died four months after discharge).

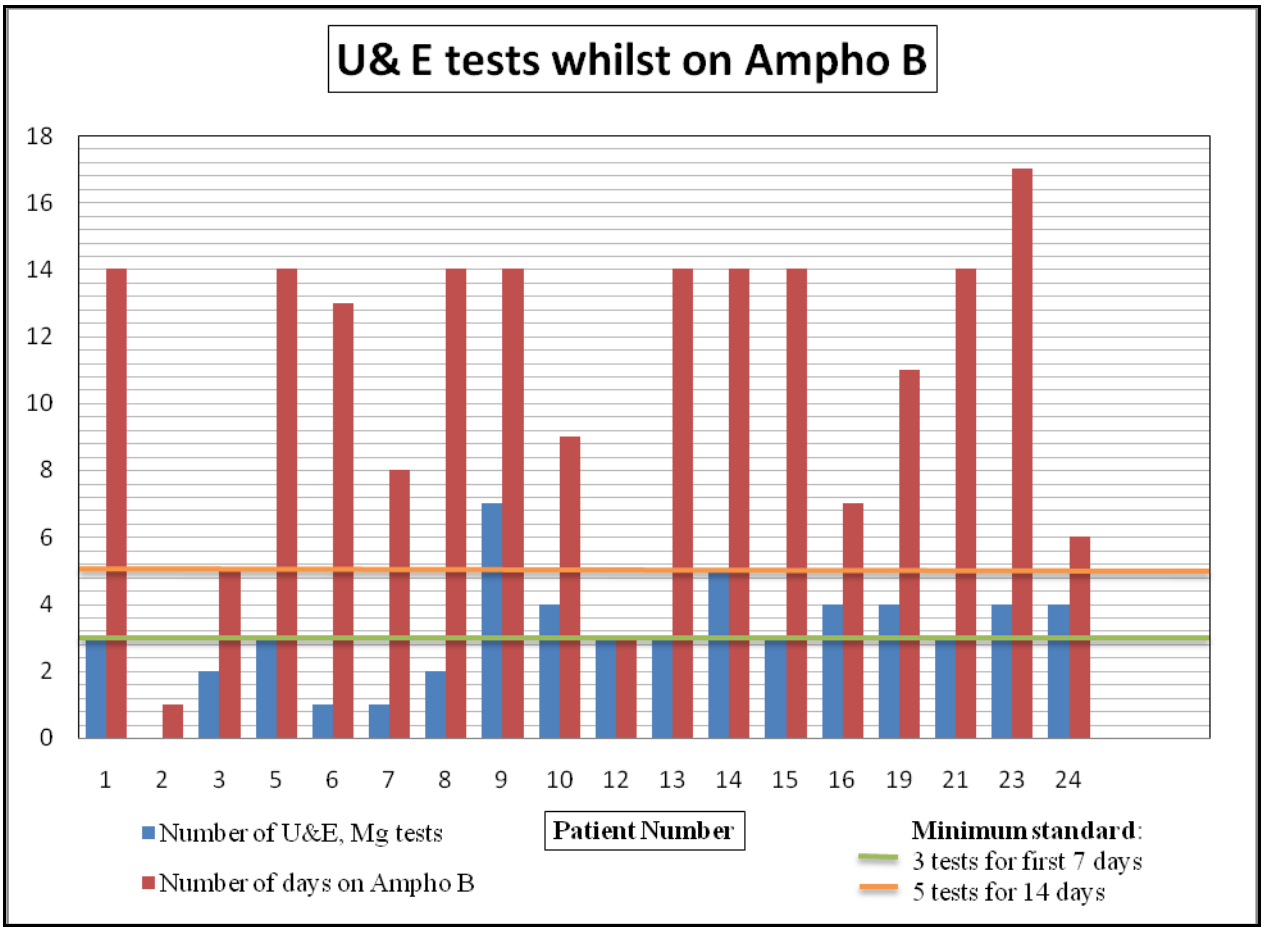
5.6 Renal (Urea, Creatinine and Electrolytes) monitoring whilst on Ampho B

Criterion 2.7 looked at the average number of Urea, Creatinine and Electrolytes (U&E and Mg) tests whilst on Amphotericin B (initial and 2 tests/week).

During the standard fourteen-day Amphotericin B treatment period, the audit team would like to see an average of five U&E and Mg tests performed on each patient (one initial value and two tests per week, if no abnormal findings – with abnormal test results, the tests should be performed more often).

Therefore, by the end of week one, three tests should have been done and by the end of week two, five tests should have been done.

Figure 9: Adequacy of number of U&E tests whilst on Ampho B (All patients exposed to Ampho B, excluding one patient who was an inpatient at time of data analysis and two patients with no record of U&E tests; one patient received 17 days of Ampho B)



The unexpected finding was that patient 23 was exposed to seventeen days of Ampho B. A closer look at the clinical notes revealed that this patient was exposed to two different doses of Ampho B durung this period and that the minimum standard of renal monitoring was not met. The patient died one day after completion of Ampho B. The exact cause of death was unclear from the clinical notes.

The Ampho B course of patients 3, 6 and 10 was stopped due to Ampho B related renal impairment. Patients 6 and 10 did not meet the minimum standard of renal monitoring. According to the clinical records, these patients did receive saline pre-loading prior to the daily Ampho B dose. One could, however, argue that adhering to the standard of renal monitoring may have enabled the clinical team to identify renal function deterioration sooner and increased the intravenous fluids. Unfortunately, the data capturing tool did not record the Creatinine values of the U&E tests done. This may have provided the researcher with an improved ability to interpret the results (if the Creatinine value had doubled, the SA HIV Clinician guidelines recommend the omission of one dose of Ampho B).

Table 7: Adherence to minimum standard of renal monitoring whilst on Ampho B

Minimum standard = three tests for first seven days and five tests for fourteen days

	Number of Patients
Adherent to minimum standard	**8**
Not Adherent to minimum standard	**10**

Of those patients where the course of Ampho B was interrupted due to Ampho B related renal impairment: in two out of three patients there was adherence to the minimum standard.

5.7 ART Referral Data

Table 8 explains why certain folders were excluded from the evaluation of Anti-Retroviral Treatment (ART) referral process. Those patients already on ART, inpatients (at time of data analysis) and patients who died as inpatients, were excluded from the analysis. The researcher wanted to evaluate the patients who were in the fourteen-day inpatient period, in which the guidelines recommend referral for ART counselling and assessment.

Table 8: ART Referral Data

Patient data eligible for analysis of ART referral process	Total	Breakdown
Total Patient Files / Clinical records	**25**	
Exclusion:	**14**	
Inpatient Death prior to and whilst on Ampho B		9
Patients already on ART at time of CM diagnosis		2
Current inpatient status (2 patients have completed Ampho B)		3
Inclusion:	**11**	
Inpatient Death after 14 day Ampho B completion		3
Inpatient care: alive until discharge date		7
Patient previously on ART, but who has defaulted treatment		1

5.8 Comparison of Level of Performance to Target Standard for Total Study Population

The following table represents the calculation process of the actual level of performance of each criterion for the **whole study population**. This level is compared to the target standard.

Table 9a: Comparison of Level of Performance to Target Standard (N = Total Population)

	Criteria:	***Value***	***Target Standard***	***Actual Performance***
		Structure		
1.1	Availability of Amphotericin B	Five patients' Ampho B interrupted due to no stock (twenty patients on Ampho B) Therefore: 15/20 = **75%**	100%	**75%**
1.2	Availability of Fluconazole	**100%**	100%	**100%**
1.3	Protocol for the administration of Amphotericin B in the two wards	One hospital inadequate display of posters in ward Therefore: 4/5 hospitals = **80%**	100%	**80%**
1.4	Consistent Availability of Formal Spinal Manometers	2/5 hospitals = **40%**	80%	**40%**
		Process		
2.1	CT scan **if** depressed Level of Consciousness/Focal Neurology	2/2 patients who met criteria = **100%**	100%	**100%**
2.4	Requesting CLAT on Indian ink-negative CSF samples	8/25 patients: Indian ink negative All eight patients had CLAT test done = **100%**	100%	**100%**
		CSF Manometry		
2.2	Use of CSF manometry in initial LP's	11/25 = **44%**	100%	**20%**
2.3	Follow-up Manometry post-CM diagnosis (= at least one reading recorded during admission, including initial LP)	20/25 = **80%**	80%	**80%**

	Criteria:	***Value***	***Target Standard***	***Actual Performance***
Amphotericin B treatment process – See Table 5a (excluding one current inpatient, one patient with prior renal impairment and three inpatient deaths prior to start of Ampho B; therefore twenty patients were exposed to Ampho B)				
2.5	Completing target of fourteen days of IV Amphotericin B	9/20 = **45%**	80%	**45%**
2.6	Using correct dose of Ampho B (1mg/kg)	19/20 = **95%**	100%	**95%**
2.7	Adherence to minimum standard of renal monitoring: Average number of U&E, Mg tests whilst on Ampho B *(two patients had no recorded data in records)*	8/18 adherent to minimum standard = *Target standard* Three tests for first seven days and five tests for fourteen days **See Figure 8**	100%	**44%**
2.8	Saline preload prior to daily Ampho B dose	Two patients: No; One patient: No data Therefore: Yes/recorded in 17/20 patients = **85%**	100%	**85%**
2.9	Saline IV flush after daily Ampho B dose (sparsely documented – challenge to interpret)	Three patients: No; Five patients: No data Therefore: Yes in 12/20 patients = **60%**	100%	**60%**
ART work-up process				
2.10	Referral for inpatient ART counselling (at any time during admission)	**See Table 8** **9/11 = 81%**	80%	**81%**
	Number of inpatient ART counselling sessions (*not for audit purposes*)	Thirteen sessions for eleven patients (minimum 0 and maximum 5) Average = 1.2 sessions/patient		
2.11	Referral to ART clinic on discharge	Excluding twelve who died as inpatient **Therefore: 8/8 = 100%**	100%	**100%**

Criteria:		*Value*	*Target Standard*	*Actual Performance*
Consolidation phase of CM treatment process (including those patients previously on ART)				
2.12	High dose Fluconazole for eight weeks (consolidation phase)	Excluding eleven who died as inpatient, one patient who died within eight weeks post discharge, one patient less than two months post discharge at time of audit three inpatients at time of data analysis, two patients: no data available **Therefore: 7/7 = 100%**	100%	**100%**
Outcome				
3.1	Commencement of ART by week four into antifungal treatment	At CM diagnosis: 20/25 were not on ART (including 1 treatment interrupter) **Of these 20:** Two were inpatients at time of data analysis Twelve died as inpatient One patient had no available data **Therefore: 3/5 = 60%**	80%	**60%**
3.2	Morbidity: incidence of Ampho B associated renal impairment	Three documented cases that were significant enough for the treating team to stop course of Ampho B **3/20 = 15%**	<20%	**15%**
3.3	Morbidity: Ampho B associated thrombophlebitis	Two documented cases: **2/20 = 10%**	<10%	**10%**
3.4	Two month-survival post-diagnosis *Three were inpatients at time of data analysis* *Four patients: no data available*	*Eleven died as inpatient* *One patient died after discharge* Six patients alive two months post-diagnosis **Therefore: 6/18 = 33% of patients alive two months after CM diagnosis**	60%	**33%**

Table 9b

Comparison between the Target Standard and the Actual Level of Performance (total study population)

The criteria that meet the target standards are displayed in green and those that require improvement are highlighted in red.

Criteria	***Meeting Target Standard***	***NOT Meeting Target Standard***
Structure	1.2 Availability of Fluconazole	1.1 Availability of Amphotericin B
		1.3 Protocol for the administration of Amphotericin B in wards
		1.4 Availability of Spinal Manometers
Process	2.1 CT scan **if** depressed Level of Consciousness/Focal Neurology	2.2 Use of CSF manometry in all initial LP's
	2.4 Requesting CLAT on Indian ink-negative CSF samples	2.5 Completing target of fourteen days of IV Amphotericin B
	2.3 Follow-up Manometry post-CM diagnosis when raised OP with initial LP or symptoms of raised ICP	2.7 Adherence to minimum standard of renal monitoring
	2.6 Using correct dose of Ampho B (1mg/kg)	2.8 Saline preload prior to daily Ampho B dose
	2.10 Referral for inpatient ART counselling	2.9 Saline IV flush after daily Ampho B dose
	2.11 High dose Fluconazole for eight weeks (consolidation phase)	
	2.12 Referral to ART clinic on discharge	
Outcome	3.2 Morbidity: incidence of Ampho B associated renal impairment	3.1 Commencement of ART by week four into antifungal treatment
	3.3 Morbidity: Ampho B associated thrombophlebitis	3.4 Two month-survival post-diagnosis

5.9 Comparison of Level of Performance: Level 1 vs. Level 2 hospitals

The data of six Level 1 and fourteen Level 2 patients were used to look at the differences in structure, process and outcome in the management of CM. Level 1 refers to Ceres (CH) and Robertson (RH), whilst Level 2 refers to Worcester (WH). The researcher excluded the data from Brewelskloof (BH) for this analysis, as the average length of stay for these patients were considerably longer, as they were treated for complicated tuberculosis in sub-acute beds in a dedicated tuberculosis hospital.

The data is presented in the same format: demography, analysis of management process and, finally, comparison of level of performance between the two levels of hospital care.

Table 10: Comparison of Level of Performance: Level 1 vs. Level 2 hospitals

Table 10a: Demographics	**Level 1**	**Level 2**
Number of Patients in Audit	**6**	**14**
Average Age (years)	39	35
Average CD4 count at CM diagnosis	105	108
Average inpatient stay, if available (in days), for those patients that were discharged	20	26

Table 10b. Results: Level of Performance: Level 1 vs. Level 2

Criteria:		***Target Standard***	***Actual Performance***	
			Level 1	***Level 2***
Structure				
1.1	Availability of Amphotericin B	**100%**	One patients' Ampho B interrupted due to no stock Therefore: 5/6 = **83%**	One patients' Ampho B interrupted due to no stock Therefore: 6/10 = **60%**
1.2	Availability of Fluconazole	**100%**	**100%**	**100%**
1.3	Protocol for the administration of Amphotericin B in wards	**100%**	2/2 hospitals = **100%**	0/1 = **0%**
1.4	Consistent Availability of Formal Spinal Manometers	**80%**	0/2 hospitals = **0%**	1/1 = **100%**
Process				
2.1	CT scan **if** depressed Level of Consciousness/Focal Neurology	**100%**	**100%**	**100%**
2.4	Requesting CLAT on Indian ink-negative CSF samples	**100%**	1/6 patients: Indian ink negative This patient had CLAT test done = **100%**	3/14 patients: Indian ink negative 3/3 patients had CLAT test done = **100%**
CSF Manometry				
2.2	Use of CSF manometry in initial LP's	**100%**	1/6 = **17%**	5/14 = **36%**
2.3	Follow-up Manometry post-CM diagnosis (= one reading recorded during admission)	**80%**	3/6 = **50%**	13/14 = **93%**

Criteria:		*Target Standard*	*Actual Performance*	
			Level 1	*Level 2*
Amphotericin B treatment process				
2.5	Completing target of fourteen days of IV Amphotericin B	**80%**	2/5 = **33%**	5/11 = **45 %**
2.6	Using correct dose of Ampho B (1mg/kg)	**100%**	5/5 = **100%**	10/11 = **91%**
2.7	Adherence to minimum standard of renal monitoring (initial and two/week)	**100%**	2/5 Adherent **= 40 %**	4/9 Adherent **= 44%**
2.8	Saline preload prior to daily Ampho B dose	**100%**	One patients: No Yes recorded in 4/5 patients = **80%**	One patient: No; One patient: No data Yes recorded in 9/11 patients = **81%**
2.9	Saline IV flush after daily Ampho B dose	**100%**	3 patients: No; Therefore: Yes in 2/5 patients = **40%**	1 patients: No; 5 patients: No data Therefore: Yes in 5/11 patients = **45%**
ART work-up process: Eligibility criteria similar to district study population evaluation				
2.10	Referral for inpatient ART counselling (at any time during admission)	**80%**	**3/3 = 100%**	**5/7 = 71%**
	Number of inpatient ART counselling sessions (*not for audit purposes*)		1 session for 3 patients (minimum 0 en maximum 1) Average = 0.3 sessions/patient	6 sessions for 5 patients (minimum 0 en maximum 2) Average = 1.2 sessions/patient

Criteria:		*Target Standard*	*Actual Performance*	
			Level 1	*Level 2*
2.12	Referral to ART clinic on discharge	**100%**	Excluding three who died as inpatient **Therefore: 3/3 = 100%**	Excluding twelve who died as inpatient and two currently inpatient **Therefore: 5/5 = 100%**
Consolidation phase of CM treatment process (including those patients previously on ART)				
2.11	High dose Fluconazole for eight weeks (consolidation phase)	**100%**	Excluding two who died as inpatient, one patient who died within eight weeks post discharge, **Therefore: 3/3 = 100%**	Excluding seven who died as inpatient, two inpatients at time of data analysis, two patients: no data available **Therefore: 3/3 = 100%**
Outcome				
3.1	Commencement of ART by week four into antifungal treatment	**80%**	At CM diagnosis: 4/6 were not on ART **Of these four:** One died as inpatient **Therefore: 1/3 = 33%**	At CM diagnosis: 14/14 were not on ART (including 1 defaulter) **Of these fourteen:** two were inpatients at time of data analysis seven died as inpatient one patient has no available data **Therefore: 2/6 = 33%**

Criteria:		***Target Standard***	***Actual Performance***	
			Level 1	***Level 2***
3.2	Morbidity: incidence of Ampho B associated renal impairment	**20%**	Two documented cases that were significant enough for the treating team to stop course of Ampho B **2/5 = 40%**	Zero documented cases that were significant enough for the treating team to stop course of Ampho B **0/11 = 0%**
3.3	Morbidity: Ampho B associated thrombophlebitis	**10%**	Zero documented cases: **0/5 = 0%**	One documented case: **1/11 = 9%**
3.4	Two month-survival post-diagnosis	**60%**	Zero were inpatients at time of data analysis 0 patients: no data available *Two died as inpatient* *One patient died after discharge* Three patients alive two months post-diagnosis **Therefore: 3/6 = 50% of patients alive two months after CM diagnosis**	Two were inpatients at time of data analysis Three patients: no data available *Seven died as inpatient* *Zero patient died after discharge* Two patients alive two months post-diagnosis **Therefore: 2/9 = 22% of patients alive two months after CM diagnosis**
Performance **meeting target standards**			Performance **not meeting target standard**	

The eligibility criteria for evaluating the Ampho B treatment process were similar to total study population evaluation.

5.10 Comparison of Level of Performance: Worcester Regional Hospital: Pilot Audit (2008) vs. Re-Audit (2010)

The findings of the two audits at Worcester hospital are compared.

Table 11a. Demographics: Worcester Hospital Audits (2008 and 2010)

Table 11a. Demographics	**2008**	**2010**
Number of Patients in Audit	**13**	**14**
Average Age (years)	35	35
Average CD4 count at CM diagnosis	110	108
Average inpatient stay, if available (in days), for those patients that were discharged	No data	26
Number of Patients on with previous diagnosis of CM	2	0
Number of Patients already on ART at CM diagnosis	3	0

Table 11b. Comparing of actual performance of WH (2008 vs. 2010) to the target standards

***Criteria* (from the pilot audit)**			***Level of Performance***	***Actual Performance:* 2008**	***Actual Performance:* 2010**
Structure	1.1	Availability of Amphotericin B	100%	100%	**60%**
	1.2	Availability of Fluconazole	100%	100%	100%
	1.3	Protocol for the administration of Amphotericin B in ward	100%	**50%**	**0%**
Process	2.4	Requesting CLAT on Indian ink-negative CSF samples	100%	100%	100%
	2.7	Baseline U&E and biweekly U&E	100%	**92%**	**44%**
	2.1	CT scan if depressed Level of Consciousness/Focal Neurology	100%	**75%**	**100%**

***Criteria* (from the pilot audit)**			***Level of Performance***	***Actual Performance:* 2008**	***Actual Performance:* 2010**
Process: *continued*	2.2	Use of CSF manometry in all LP's	100%	**23.1%**	**Initial LP: 36%** **Follow-up Manometry: 93%**
	2.5	Completing target of fourteen days of IV Amphotericin B	80%	77.8%	**45%**
	2.12	High dose Fluconazole for eight weeks (consolidation phase)	100%	100%	100%
		Adherent to long-term Fluconazole (secondary prophylaxis)	80%	**71.4%**	**Not measured**
	2.13	Referral to ART clinic	100%	100%	100%
	3.1	Commencement of ART by week four into antifungal treatment	80%	**0%**	**33%**
Outcome	3.2	Morbidity: incidence of drug-induced renal impairment (Amphotericin B)	20%	0 – 15% (i.e. <20%)	0%
	3.4	Two month-survival post-diagnosis	60%	**46.2%**	**22%**

Performance showing improvement and **meeting target standard**	Performance showing improvement, yet still **not meeting target standard**	Performance worse than previous audit and **not meeting target standard**

6. Discussion of Results

The results are evaluated in light of the literature reviewed. Furthermore, it is essential to evaluate if the objectives of the audit were met. The results are discussed in three sections: the total study population, the comparison of the Level 1 vs. Level 2 hospitals and the comparison of the pilot audit (2008) vs. re-audit (2010) at the regional hospital.

6.1 Total Study Population (N = 25) – Cape Winelands (East) District

The two sections of findings are illustrated in green (areas of good practice: meeting target standards) and in red (areas in need of improvement: not meeting target standards).

Performance **meeting target standards**	Performance **not meeting target standard**

6.1.1 Areas of good practice:

Only one structure-related criterion, the availability of Fluconazole, was sufficient (criterion 1.2).

In terms of process, CT scans were ordered when indicated (criterion 2.1). The clinical team was aware of the need to perform CSF manometry (criterion 2.3) once the diagnosis of CM was made. CLAT tests were ordered on Indian ink negative CSF samples (criterion 2.4). The correct dose of Ampho B was prescribed (criterion 2.6) and inpatients were referred for ART counselling (criterion 2.10). On completion of the Ampho B course, patients were started on high dose Fluconazole (consolidation phase) (criterion 2.11) and, on discharge, patients were referred for follow-up at the ART clinic (criterion 2.12).

The outcome-based criteria, renal impairment (criterion 3.2) and thrombophlebitis (criterion 3.3) associated with Ampho B treatment, were within acceptable levels (literature-based target standards were achieved).

6.1.2 Areas in need of improvement:

The availability of Amphotericin B, spinal manometers and ward protocols were inconsistent (criteria 1.1, 1.3 and 1.4). An unexpected finding was the interruption of treatment due to no Ampho B stock. The researcher has conducted an informal interview with the main pharmacist. It seems that there may be a delay when ward staff fail to order stock in time. This issue needs further exploration at local and regional Pharmaceutical Treatment Committee (PTC) meetings.

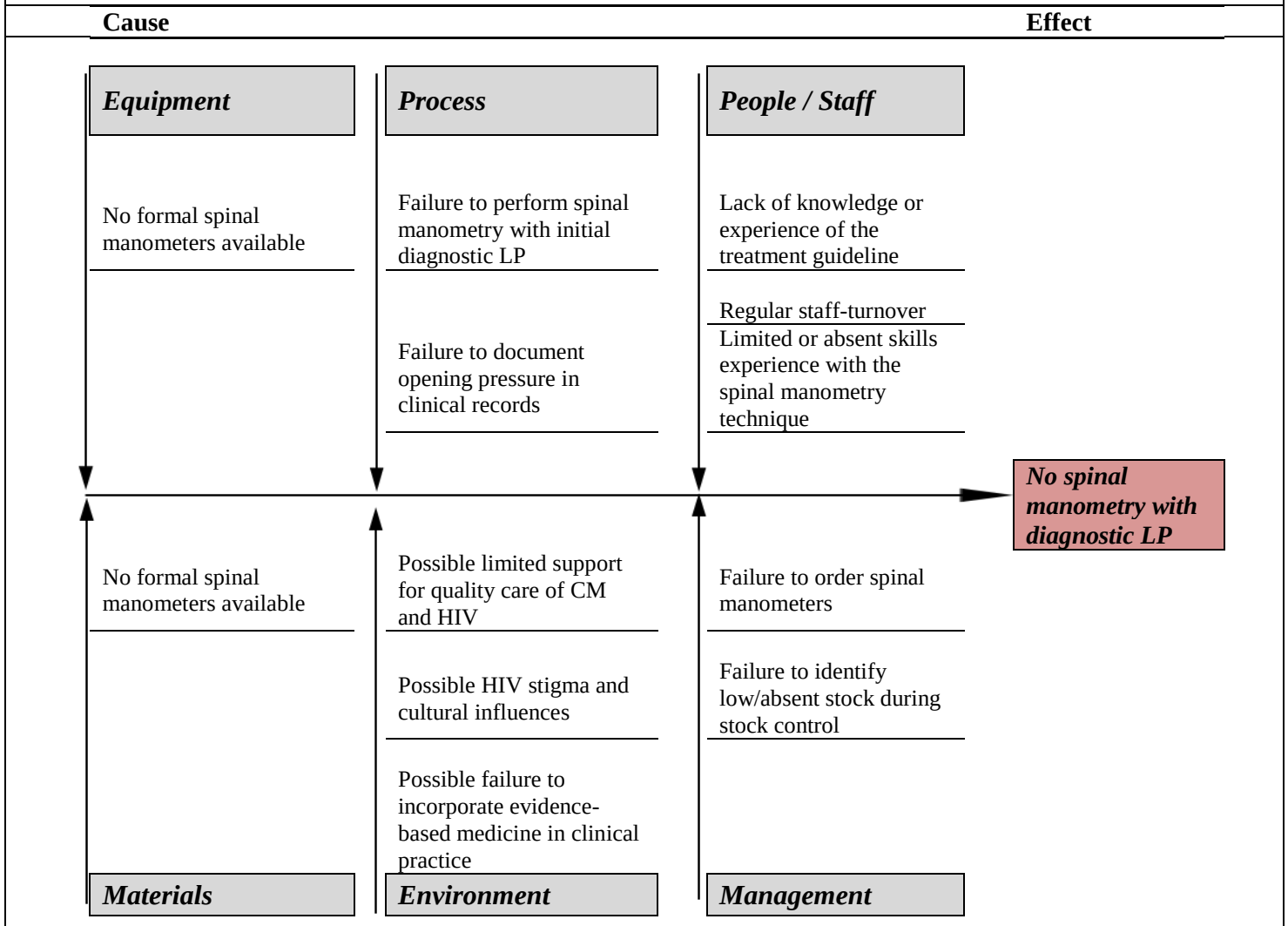
There was a paucity of spinal manometry measurements with initial lumbar punctures (criterion 2.2). Reasons for non-adherence to this criterion require analysis. The fishbone diagram (Figure 10) examines possible causes in the following categories: Equipment and Materials, Process, Environment, People/Staff and Management. A comprehensive approach is required to address the multi-factorial issues regarding this criterion, especially the issue of staff-turnover (interns and junior medical officers rotate through departments).

The guidelines recommend subsequent manometry measurements in those patients who had a raised reading. It may be speculated that clinical factors such as absence of raised ICP signs and absence of headache may have influenced the treating doctor to withhold follow-up manometry measurements.

Reasons for failing to reach the fourteen-day Ampho B target (criterion 2.5) were highlighted in the pie chart (Figure 8). There were three main reasons: patient death, drug stock problem, renal impairment. The monitoring of Ampho B treatment was also sub-optimal. Reasons for failing to attain the minimum number of U&E tests (criterion 2.7) require exploration. Possible causes for sub-standard renal monitoring include location of laboratory services and awareness of need to monitor renal function. The NHLS laboratory is located adjacent to Worcester hospital. Access to laboratory services after-hours is a potential problem at the district hospitals. However, a courier service collects laboratory specimens twice a day (during office hours) at each district hospital.

Figure 10: Cause and Effect Fishbone Diagram

Failure to perform or document spinal manometry with initial lumbar puncture (LP) in patients with Cryptococcal Meningitis (CM)



Saline preload prior to Ampho B dose (criterion 2.8) and saline flushing of line after Ampho B dose (criterion 2.19) requires renewed emphasis (including the need to emphasise the importance of documenting these steps of the management protocol). These criteria were poorly documented in the clinical notes.

The challenge to start patients with CM on ART within four weeks from onset of antifungal treatment (A2A period = Ampho to ART period), seems to be an ongoing one (criterion 3.1). A cause and effect Fishbone diagram may be of use to evaluate causality.

The two-month survival figure of CM patients is still below the Sub-Sahara reference value (criterion 3.4) – this will warrant further exploration. Factors that predict higher mortality should guide the clinical team in directing more attention to guideline-based care. These negative-predictive factors regarding mortality-risk include high CSF fungal burden, raised intracranial pressure, low CD4 count and other co-morbid factors. [43]

6.2 Comparison Level 1 and Level 2:

Performance **meeting target standards**	Performance **not meeting target standard**

The researcher needs to emphasise the small size of the study population. Furthermore, there are important differences between the package of care of Level 1 (generalist-led care) and Level 2 (specialist-led care). However, there are certain themes that may be examined in the correct, non-judgmental light: the two levels of care represent a continuum of care in one district and both services depend on each other. The following themes describe the clinical relevance of the audit findings:

Spinal manometry (process) is performed more consistently in the Level 2 hospital than in the Level 1 hospitals; spinal manometers (structure) are also consistently available at the Level 2 hospital. Spinal manometers were introduced to the sub-district management and procurement departments of the district hospitals prior to the audit period (this intervention coincided with the teaching activities). However, the manometers were not readily available at the district hospitals. The clinical use of the manometers (by doctors) and stocking of manometers (management and procurement department) need to be re-emphasised.

The adherence to renal monitoring of patients on Ampho B (U&E, Mg) is lacking in both settings and fails to meet the target standard. At Level 1, access to laboratory services is comparable to the Level 2 hospital during office-hours (when U&E tests are typically done), as a courier service collects laboratory specimens twice a day at each district hospital. Saline preloading is done well in both settings, however saline flushing of the line after the Ampho B dose is poorly documented in both settings. The importance of clear and complete clinical record keeping should be addressed with the next intervention.

The inpatient referral for ART counselling is more consistent in the Level 1 setting, however both levels of care have difficulty in achieving the target of four weeks between onset of Ampho B and onset of ART. The barriers to this process require further analysis (ART work-up, social assessment and other factors may need consideration).

Both settings report a low prevalence (over the data collection period) of Ampho B related morbidity (but documentation of these side-effects were consistently sparse in both settings).

The two-month survival figure fails to meet the target standard in both settings; there has been a worsening in survival at Level 2 compared to the pilot audit in 2008 (discussed in the next section).

In summary, this comparison between the two levels of care makes it possible to recommend that Level 1 hospitals continue to manage CM patients. The availability and use of spinal manometers, and closer adherence to renal monitoring will support this recommendation. Arrangement of inpatient ART counselling happened more consistently at the Level 1 hospital. Adherence to the ART target and measures to prevent Ampho B related morbidity is comparable to that of the Level 2 hospital.

6.3 Comparison Pilot Audit (2008) vs. Re-Audit (2010) at Level 2 hospital (Worcester):

The table demonstrates the findings in the “traffic light” colour scheme:

Performance showing improvement and **meeting target standard**	Performance showing improvement, yet still **not meeting target standard**	Performance worse than previous audit and **not meeting target standard**

This visual guide is an effective way to inform the audit team (and reader) of areas of good

practice and areas for improvement. The colour orange/yellow is used to highlight those areas that have improved, but are still not meeting the target standards.

Of interest is the similarity between the demographics of the two audit groups (age and CD4 count): see Table 11a.

In terms of structure, the availability of Ampho B stock has been inconsistent during the re-audit period. This represents a new (and unexpected) finding. As mentioned, this issue requires further exploration at local and regional Pharmaceutical Treatment Committee (PTC) meetings.

The availability of a ward-based CM treatment protocol (poster and guidelines) have been lacking in both audits. Surprisingly, this occurred after the researcher has distributed laminated posters with treatment guidelines (Addendum 6) together with the teaching intervention.

In terms of process, the attention to renal monitoring in Ampho B exposed patients has decreased in the re-audit period. This is likely to be a multi-factorial based problem that needs to be addressed during the feedback phase to the audit team.

The re-audit has shown an improvement in adherence to the CT scan indication standard. This may be attributed to the acquirement of a CT scanner at Worcester hospital during the data collection period.

The overall attention to spinal manometry has improved considerably in the re-audit period; the adherence to the use of manometry with the initial (diagnostic) LP needs to be re-addressed.

The re-audit period has shown a decline in achieving the fourteen-day Ampho B goal. As mentioned, this was likely to be caused by the Ampho B stock issue and the higher mortality rate in the re-audit group.

There has been an improvement in reaching the four-week Ampho B to ART goal. The factors that led to this improvement (clinical significance) require exploration, identification and re-enforcement. Similarly, the worsening of the two month-survival post-diagnosis figures needs exploration to identify possible correctable causes (clinical management factors, health care provider factors, patient factors and health system factors). The process of continuous quality improvement involves re-enforcement of what is done well and intervention in what is done poorly.

6.4 SWOT Analysis of Audit experience

The researcher has experienced the continuous learning curve that is essential with any project of this size. A SWOT analysis is a "strategic planning method used to evaluate the Strengths, Weaknesses, Opportunities, and Threats involved in a project." [44] This process will help to evaluate the audit.

- **Strengths**
    - The audit team consisted of key individuals at each hospital. The researcher maintained contact with the rest of the team via face-to-face meetings (individual and group), telephonic conversations and email communication (see Addendum 8 for an example of such an email). The importance of teamwork was highlighted.
    - Partnership and interaction with NHLS laboratory: the researcher enjoyed good support, especially in terms of obtaining the list of folder numbers that were coupled with CM tests during the audit period.
- **Challenges and Pitfalls (Weaknesses)**
    - The prospective data collection process failed, especially at Worcester hospital: no data capturing forms were completed at Worcester during the audit period. The researcher was aware of this problem and attempted to remind the clinical team of the audit process. This has led to under-reporting of cases. In the future, alternative data collection processes should be explored.
    - The challenge of collecting data in patients transferred to different hospitals, especially to hospitals outside district: these cases were excluded, as they were managed at hospitals that were not included in the audit.
    - At Worcester hospital, the ward where most of the CM patients were treated, struggled to provide continuity of care. This proved to hamper the audit process (adherence to guidelines and data collection). Factors that had a negative influence included staff factors (regular staff turnover and level of seniority/experience) and structural factors (no CM management posters and no

CM Audit documents were found on inspection). The level of seniority/experience of the treating doctor may possibly influence the adherence to the CM treatment steps. It should also be noted that the teaching intervention was held at the end of the calendar year. New interns and community service doctors (junior doctors) started to work at both Level 1 and 2 hospitals in January 2010. The researcher discussed the option of a follow-up teaching intervention with the audit team, but it was suggested that the audit champions of each hospital should orientate the new doctors regarding the CM audit process (treatment guidelines and data capturing forms).

- Clinical records: as mentioned, some notes were incomplete and this hampered the team's ability to analyse the data.

- The unexpected finding of the Ampho B stock shortage needs attention in the feedback process and planning of the next intervention.

- Also unexpected was the finding that three patients were discharged from the casualty department prior to CSF CLAT result availability (the researcher has contacted the clinical team and a follow-up review of these patients was arranged). CLAT tests take three to five days. Therefore, an improved follow-up system should be arranged on discharge with the primary care or ART clinic (if the patient meets discharge criteria). Local discharge criteria require review.

- The issues of spinal manometer availability and adherence to manometry have been explored. Alternative options of measuring raised ICP were employed: crude opening pressures were measured with regular intravenous lines; this is a non-standardised and inaccurate way of measuring the opening pressure. It may provide and estimate of raised ICP and the need for a therapeutic tap to relieve such pressure. However, the gold standard remains a standardised spinal manometer (cheaper models are available that may match the costs of intravenous lines). Possible supply chain issues of procurement should be explored.

- **Opportunities**
    - This audit has the inherent ability to improve CM care and outcome, reduce Ampho B-related morbidity and improve access to ART.
    - If implemented and continued correctly, with the necessary buy-in and support of stake-holders, a culture of quality awareness may be created. This may lead to further audits and QI initiatives in various aspects of care.
- **Threats**
    - Lack of resources (including human resources, time and management support) may hamper the process of establishing a culture of quality improvement.
    - Failure to re-audit the management of CM in HIV adults in the Cape Wineland (East) district, may lead to a missed opportunity to address the gaps identified by this audit.

6.5 Possible Confounding factors

The following factors should be considered during the evaluation of the audit findings

- The influence of the teaching intervention may be confounded by the annual change-over of clinicians: a new set of doctors replaced some of the doctors at the beginning of the calendar year (new interns and community service doctors). The formal teaching interventions were held during September and October of 2009. Clinical guidelines were available in the wards and senior doctors were present at the teaching sessions. The new set of doctors may have previous clinical experience of the management of CM.
- The adequacy of clinical record keeping (doctors and nurses) in certain folders has made it challenging to audit the criteria.

6.6 Discussion of Quality Improvement tools

The most important part of the audit is the ability to enable change. The change process involves three stages:

1. Initiation (change analysis: stakeholder analysis: enabling buy-in)
2. Implementing change (action plan: intervention)
3. Continuing the process (re-audit to confirm improvement). [6]

Various Quality Improvement tools/instruments (with the common goal of closing the gap between evidence-based medicine and routine practice) have been described. The audit team will need to consider new strategies when planning the intervention. A list of six general categories is provided, but usually a multi-modal approach is required:

1. provider education
2. provider reminder systems and decision support
3. audit and feedback
4. education of patients
5. organisational change
6. financial incentives, regulation, and policy

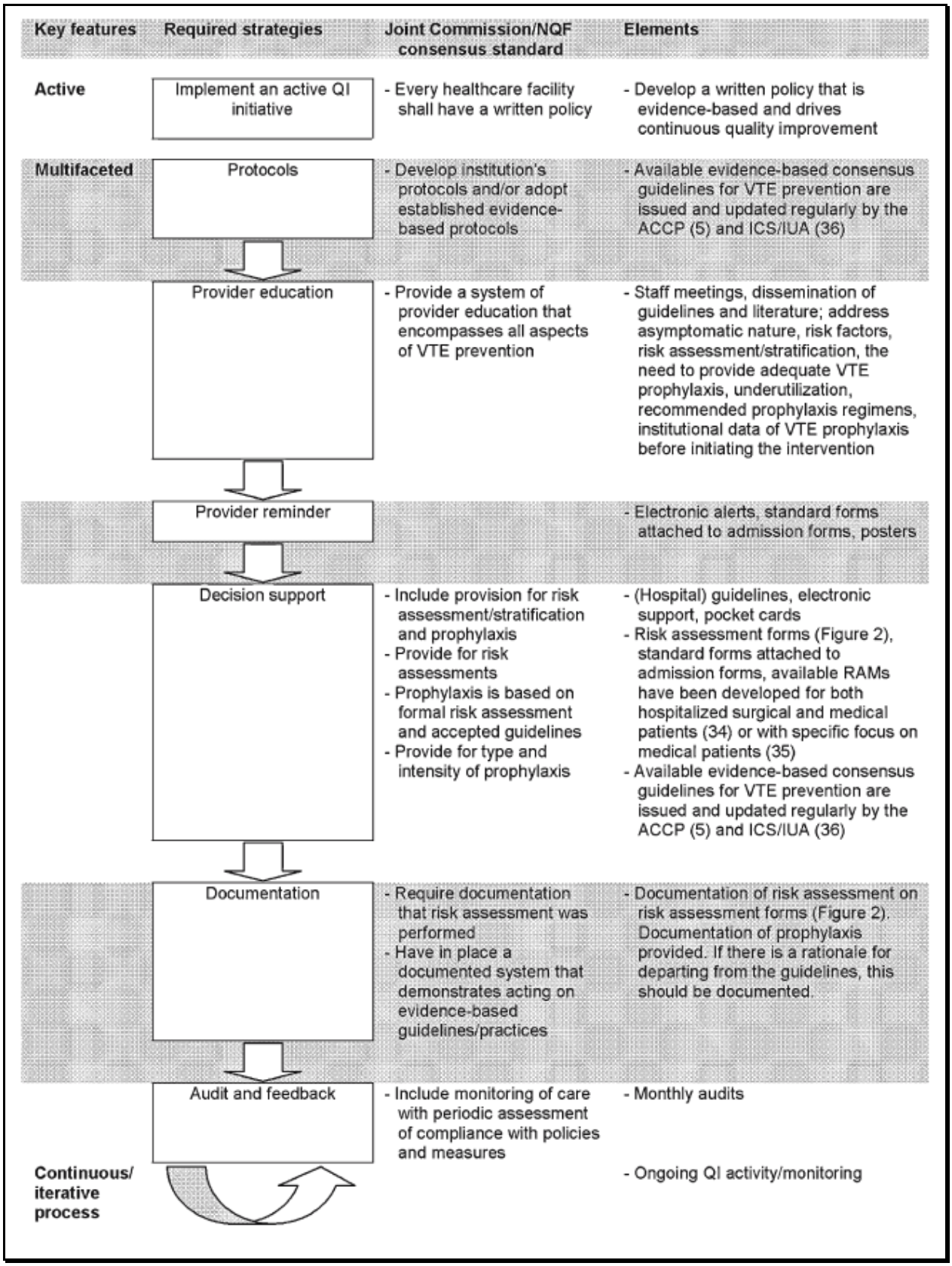
The key features of an effective strategy for improving care are:

- an active strategy
- a multifaceted/multimodal approach
- a continuous process of improvement

The application of these principles in enabling change, will be discussed in the recommendations.

Figure 11 provides an example of a multimodal QI strategy: this multimodal strategy was aimed at improving venous thromboembolism (VTE) prophylaxis, based on the Joint Commission/ National Quality Forum (NQF)-endorsed consensus standards. (Abbreviations in Figure: ACCP - American College of Chest Physicians; ICS - International Consensus Statements; IUA - International Union of Angiology; QI - quality improvement; RAMs - risk assessment models) [45]

Figure 11: Example of a multimodal QI strategy [45]



7. Recommendations

The recommendations will be discussed in two sections: those recommendations for future cycles of the CM audit; and, recommendations for audits in general, specifically in the public health sector of South Africa.

7.1 Recommendations for future cycles of CM audit process:

A dedicated audit team with clear task delegation is required at each site. Each setting should explore ways to encourage buy in and empowerment of health care workers.

7.1.1 Feedback Phase of Audit and Feedback QI instrument:

The researcher is planning formal feedback sessions to the audit team and the health care workers at the hospitals involved.

A meta-analytic study has explored the applicability of the Feedback Intervention Theory (a framework from industrial/organizational psychology) in health care Audit and Feedback. One example of how feedback may be maximally effective, is the emphasis that the recipient should be focused on the task. Frequent, individualised, and non-punitive feedback has been shown to be effective in helping primary care providers adhere to clinical practice guidelines. [46]

7.1.2 Next step of the cycle: considering a new intervention

An Integrated Clinical Pathway (iCP) may improve the clinical team's management approach by providing a clear systematic treatment plan for **each** patient admitted with CM:
"(Integrated care pathways) are **multidisciplinary**, **locally agreed**, **evidence-based** *plans*, describing the **expected progress** of a *specific* patient group. They form **all** or **part** of the **clinical record**. By facilitating the **evaluation of outcome**, they can be a quality improvement tool for use as part of **clinical governance.**" [47]

Such an iCP should be based on the SA HIV Clinician Society guidelines and the recently published 2010 IDSA (Infectious Diseases Society of America) CM management guidelines. [19, 48]

It has been shown that a strategy that involves developing and disseminating local hospital guidelines may be more effective than passive dissemination of national or international guidelines. [24] iCPs have resource implications: all new staff will require induction. Current staff will require ongoing training. [47]

The researcher has composed a draft iCP (Addendum 10), which will be presented to the clinical and audit team for discussion and approval. The iCP incorporates the audit criteria, which may streamline future follow-up audits (re-audits). The iCP may enable the team to keep a CM data base/ data register.

While the iCP acts as a template of the care to be provided to the chosen group of patients, it is not intended to compromise clinical judgment. Members of the clinical team may deviate from the pathway if there is a valid reason. Analysis of variations from the pathway provides information to the clinical team on the overall quality of care and helps to identify any trends that may require further investigation. iCPs are dynamic documents: change is to be expected as new evidence and clinical guidelines emerge. [49]

7.1.3 Review of the steps of the Audit Process

The audit team should review the factors that influenced the steps of this audit. It is clear that close liaison with the NHLS Laboratory is essential.

An iCP may augment the clinical notes and facilitate the data capturing process of the individual criteria (this will address the issue of paucity of clinical notes).

Aspects of Structure, especially Spinal Manometers, need to be re-addressed prior to commencing a further audit cycle: liaison with the supply chain (procurement involvement) of the hospital administration and hospital management will be essential.

A CM database or data register (with the aid of the Laboratory, ART clinic and iCP) may enable the audit team to improve the quality of data for subsequent audits. This database may also be utilised for other forms of research (with the necessary ethics committee approval), such as long term follow-up, evaluation/audit of adherence to Fluconazole and/or ART, the incidence of CM IRIS and CM Fluconazole resistance.

7.1.4 CM prevention (primary prevention)

Ultimately, a primary prevention/screening approach should be envisaged, compared to the standard curative approach. The focus should be on primary prevention and exploring the reasons (social and cultural) why patients present to health institutions in the advanced stages of HIV/AIDS and opportunistic infections.

The TB/HIV service integration within the primary health care system (and acceptance of HIV/AIDS as a chronic illness) may enable this paradigm shift.

The following aspects of care need support:

- Screening for HIV in patients: early access to diagnosis and CD4 count, early ART to prevent low CD4 and risk of Opportunistic Infections.
- Early diagnosis of CM: its atypical presentation warrants high index of suspicion.
- Attention to best practice care during A2A (Ampho B until ART) period has greatest chance on survival to ART initiation.

Renewed focus and energy aimed at educational interventions should be aimed at both health care workers and the public.

7.2 Recommendations for future audits (in general) in public sector hospitals

The central question should be posed: Who should be responsible for quality improvement? ("Whose job is it"): employer vs. employee vs. public? Ultimately, all stakeholders should be involved in the process.

A culture of Quality Improvement should be created and maintained. [28]

Hospital Accreditation with Health Quality Assurance organisations (such as the Council for Health Service Accreditation of South Africa, COHSASA) should be pursued, as this may create the necessary external motivation to conduct QI initiatives. [50]

The employer should make participation in QI activities part of health care workers' job description (an institutional intervention, as opposed to other forms of non-regulatory

incentives). This regulatory intervention is common in first world health systems, where institutional, regional and national audit support and development organisations are in place.

The audit teams may choose to adapt target standards and levels of performance to constraints faced in public health system. A balance should be sought between realistic and appropriate target standards, compared to unacceptable, sub-standard targets.

Interventions should focus on the essentials of good care ("Back to basics"): start with CQI initiatives at PHC level and focus on key areas (HIV, TB, chronic disease burden, health system improvement, equal health access). Parallel, interdisciplinary programmes should address the social determinants of health: health education, addressing crime and interpersonal violence, addressing unemployment and poverty, basic education, capacity development, community orientated care and upliftment.

8. Conclusions

This thesis represents a follow-up medical audit on the adherence to management guidelines of Cryptococcus Meningitis (CM) in the Cape Winelands (East) district, Western Cape, South Africa. This re-audit follows on a teaching intervention based on the findings of a pilot audit in 2008 at the Level 2 hospital. The audit team reviewed cases diagnosed and treated between November 2009 and June 2010. Twenty-five folders were reviewed. The clinical (not statistical) significance of the audit findings is relevant in order to achieve change in practice.

The teaching intervention aimed to increase awareness of the importance of spinal manometry in diagnosing and treating raised intracranial pressure (ICP), given the strong association between CM and raised ICP. Furthermore, the intervention stressed the need to commence early ART counselling in order to achieve the four week goal (period between commencement of Amphotericin B and start of ART).

The 2010 audit highlighted the following areas that are in need of improvement and that should be the focus of a new set of intervention strategies:

- Amphotericin B (Ampho B) stock availability
- Renal function monitoring of patients on Ampho B treatment
- Emphasis on the importance of completing the fourteen day Ampho B treatment period: the potentially avoidable factors that prohibit completion during this audit were Ampho B stock shortage and Ampho B associated renal impairment.
- Improved medical record keeping of both doctors and nurses: this audit has shown that certain aspects of the treatment process were documented poorly: saline preload and flushing the line with saline after each Ampho B dose are key examples.
- Commencement of ART by week four into antifungal treatment.
- Awareness of the high mortality level of the CM patients studied in this audit.

In terms of the quality of care of Level 1 vs. Level 2 hospitals, some important conclusions may be made:

Level 1 hospitals should continue to manage CM patients. The availability of spinal manometers and closer adherence to renal monitoring will improve the chance of achieving target standards. Arrangement of inpatient ART counselling happened more consistently at the Level 1 hospital. Adherence to the ART target and measures to prevent Ampho B related morbidity is comparable to that of the Level 2 hospital.

The comparison of the 2008 pilot audit findings with those of the 2010 re-audit at Worcester hospital showed an increased use of spinal manometry (however, the current practice needs to improve in order to meet the target standards). Patient survival has declined. Ampho B stock shortage was an unexpected non-adherent finding. The process of continuous quality improvement involves re-enforcement of what is done well and intervention in what is done poorly.

The audit has also provided insight to the researcher and audit team on the practical challenges of conducting a prospective data collection technique across different care settings (five hospitals: three Level 1 district hospitals, one regional sub-acute tuberculosis hospital and one Level 2 secondary hospital). The buy-in of stakeholders (management, health care workers and patients), the ongoing support of an audit team and a committed Quality Improvement environment will make the medical audit process feasible and care improvement possible.

Formal feedback to the clinical team and management is planned. A multimodal interdisciplinary Quality Improvement approach (such as an integrated care pathway) is recommended and a future re-audit is important to monitor improved adherence to the CM management guidelines.

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Addendum 1

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09 December 2009 **MAILED**

Dr K von Pressentin
Department of Family Medicine
3rd Floor,fisan building
Stellenbosch University
Tygerberg campus
7505

Dear Dr von Pressentin

"A prospective medical audit of the management of Cryptococcal Meningitis (CM) in HIV patients in the Cape Winelands (East) District,Western Cape,South Africa."

ETHICS REFERENCE NO: N09/08/205

RE : FINAL APPROVAL

At a meeting of the Health Research Ethics Committee that was held on 4 November 2009, the above project was approved on condition that further information is submitted.

This information was supplied and the project was finally approved on 8 December 2009 for a period of one year from this date. This project is therefore now registered and you can proceed with the work.

Please quote the above-mentioned project number in ALL future correspondence.

Please note that a progress report (obtainable on the website of our Division: www.sun.ac.za/rds should be submitted to the Committee before the year has expired. The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly and subjected to an external audit.
Translations of the consent document in the languages applicable to the study participants should be submitted.

Federal Wide Assurance Number: 00001372
Institutional Review Board (IRB) Number: IRB0005239
The Health Research Ethics Committee complies with the SA National Health Act No.61 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 Part 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

Approval Date: 8 December 2009 Expiry Date: 8 December 2010

Fakulteit Gesondheidswetenskappe · Faculty of Health Sciences

Verbind tot Optimale Gesondheid · Committed to Optimal Health
Afdeling Navorsingsontwikkeling en -steun · Division of Research Development and Support
Posbus/PO Box 19063 · Tygerberg 7505 · Suid-Afrika/South Africa
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Yours faithfully

MR FRANKLIN WEBER
RESEARCH DEVELOPMENT AND SUPPORT
Tel: +27 (0)21 938-9657 / E-mail: fweb@sun.ac.za
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Addendum 2

The Minute Paper: Feedback from Teaching Intervention

30 October 2009, Worcester Hospital

Please spend <u>one minute</u> on the following question (*Answers are kept anonymous*):

Regarding the management of Cryptococcus Meningitis patients: which aspect of your management of these patients will change after today's discussion?

Summary of Participant Responses:

- Manometry and therapeutic CSF drainage:
    - Management of raised ICP:
        - "Managing symptomatic CM: daily LPs"
        - "Asymptomatic: LPs every 2 – 3 days"
    - Early referral to neurosurgery
- Amphotericin B:
    - No longer test dose needed
    - Management of adverse reactions:
        - Saline preload before Ampho B administration (helps to prevent renal side-effects)
        - Flushing drip after Ampho B administration (helps to prevent thrombophlebitis)
- Follow-up:
    - "Will ensure adherence to secondary Fluconazole prophylaxis"
    - "Will attempt early referral for ART"
    - "Confirm referral to ART clinic – personally"
- General:
    - "Many steps changed – learned a lot" (Ampho B administration; ART referral)
    - "Will think of CM as number one cause in HIV patient with meningitis symptoms"
    - "This workshop was a fantastic, practical bridge from academic knowledge (rather faded) to the practical management of CM patients – please do this again: the other interns could also use this."

Addendum 3

Data Capturing Sheet: Cryptococcal Meningitis Medical Audit

Cape Winelands District (East) (2009 – 2010)

Please complete all areas (if possible) for each adult patient (> 13 years of age) admitted and diagnosed with Cryptococcal Meningitis (CSF Indian Ink and/or CLAT test positive).
All data will be used confidentially (use only the patient's file number). Encircle options provided where applicable. Kindly use clear handwriting. Forms are available in electronic format.

Please contact the Principal Investigator, Dr Klaus B von Pressentin, with any queries: 023-626 8040; email: klausvonp@gmail.com. **Your help with this audit is appreciated and will contribute to improved service delivery and awareness about Cryptococcal Meningitis.**

1	**Hospital / Ward**			
2	***CM Audit Number: Please contact Dr Von Pressentin to obtain Number (eg CMA 02)***			
3	**Age**			
4	**Sex**		**Male**	**Female**
5	**Date admitted**			
6	**Date discharged**			
7	**RVD status**			
8	**CD4 count**			
9	**Indian Ink result**			
10	**CLAT result / titre**			
11	**Previous CM diagnosis**		**Yes**	**No**
12	**Already on ART at time of CM diagnosis?**		**Yes**	**No**
13	**CT scan if indicated: depressed level of consciousness / focal neurology/ seizures**			
14.a.	**Use of CSF manometry (measurement of opening pressure):**	**At diagnosis**		
14.b.	**(Answer Yes/No and please provide measurement values in cmH_20 of each measurement done, where applicable)**	**Number of Follow-up CSF manometry measurements**		

15	**Dose of Ampho B used (mg/kg)**		
16	**Completing target of 2 weeks of IV Ampho B (if No: provide number of days administered)**	**Yes**	**No** **Days:**
17	**Saline pre-loading before daily Ampho B dose**	**Yes**	**No**
18.a.	**Monitoring of U&E, Mg while on Ampho B**	**Yes**	**No**
18.b.	**Number of U&E, Mg tests done while on Ampho B**		
19	**Saline flush of IV line after Ampho B dose (daily)**	**Yes**	**No**
20	**Thrombophlebitis at IV line site?**	**Yes**	**No**
21.a.	**Referral for ART counselling (as inpatient)**	**Yes**	**No**
21.b.	**Number of ART counselling sessions received as inpatient**		
22	**ID clinic appointment made (on discharge)**	**Yes**	**No**
23.a.	**Commencement of ART within 1 month (from start of antifungal treatment)**	**Yes**	**No**
23.b.	**Date of ART commencement**		
24	**High dose Fluconazole for 8 weeks**	**Yes**	**No**
26	**2 month-survival post-discharge**	**Yes**	**No**
27	**Date of death (if applicable)**		
28	**Cause of Death (if applicable)**		

List of Abbreviations:

Ampho B = Amphotericin B;

ART = Anti-retroviral Treatment;

CLAT = Cryptococcal Latex Agglutination Test

CSF = Cerebrospinal Fluid;

CT = Computer Tomography;

ID clinic = Infectious Diseases clinic

IV = Intravenous;

RVD = Retroviral Disease;

U&E, Mg = Urea and Electrolytes, Magnesium

This medical audit has been approved by the Health Research Ethics Committee of the Faculty of Health Sciences, Stellenbosch University:

Ethics Reference no: N09/08/205.

This audit will be used by the audit team to improve the health care of CM patients. The results will be used towards a thesis for an M Med degree in Family Medicine at Stellenbosch University (Supervisor: Prof HH Conradie).

Addendum 4

Patient Register: Cryptococcal Meningitis Medical Audit

Cape Winelands District (East) (2009 – 2010)

Hospital: ……

Number	*CMA Number*	Admission date	Discharge date (if applicable)	Date of Death (if applicable)	ART clinic appointment date
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					

Contact Person: Dr Klaus von Pressentin: 023-626 8040; klausvonp@gmail.com

Addendum 5: Cover document for data capturing sheet and patient register

Cryptococcal Meningitis Medical Audit

Cape Winelands District (East) (2009 – 2010)

Cryptococcus Meningitis Mediese Oudit

Kaap Wynland Distrik - Oos (2009 – 2010)

A Medical Audit of the management of Cryptococcal Meningitis (CM) in HIV patients in the Cape Winelands (East) District, Western Cape, South Africa.

Introduction:

- Cryptococcal Meningitis (CM) remains a leading cause of mortality in AIDS patients in developing countries.
- Effective treatment of increased intracranial pressure (present in at least 50% of cases) can improve outcome.
- The first 2 weeks of antifungal treatment are the most important phase of the treatment of CM, as this period could have the biggest impact on outcome.
- ART should ideally be started within 2 – 4 weeks of start of antifungal treatment for CM.

Aims and objectives of the Audit:

The aim of this medical audit (Quality Improvement Cycle) is to improve the treatment of Cryptococcal Meningitis (CM) in HIV-patients in the eastern part of the Cape Winelands District (Witzenberg, Breede Valley, Langeberg municipalities), and to improve the clinical team's awareness of and adherence to national treatment guidelines.

The objectives of the audit on the quality of care for CM in Level 1 and 2 hospitals are:

a. To create appropriate target standards
b. To demonstrate an improvement in the quality of care at the Level 2 hospital
c. To identify strengths and weaknesses at Level 1 and Level 2 hospitals
d. To identify key interventions that may improve the quality of care
e. To reflect on the quality of care at Level 1 vs. Level 2 hospitals
f. To provide feedback to the facilities and department of health

Contact Principal Investigator, Dr Klaus von Pressentin, with any queries:

Tel: 023-626 8040; email: klausvonp@gmail.com .

Ethics Reference no: N09/08/205 (HREC, Faculty of Health Sciences, Stellenbosch University)

Praktiese Riglyne t.o.v. die Oudit-proses

- **Data-insameling periode:** November 2009 - Junie 2010

- **Watter pasiënte?**

  Alle volwasse HIV-positiewe pasiënte gediagnoseer met Cryptococcus Meningitis kwalifiseer (ouderdom >13 jaar).

- **Hoe werk die vorms?**

  1. **Data insamelingsvorm (Data Capturing Sheet)**
     (2 bladsye - kan op 'n enkele A4 bladsy aan weerskante afgerol word)
     Voltooi in duplikaat:
     - Een kopie bly in die pasiënt se leêr
     - Ander kopie vergesel die pasiënt na die ART kliniek.

     Die idee is dat die data insamelingsvorm met die ontslagvorm voltooi word op die dag van ontslag.
     (Vul asb ook ‘n vorm in op die dag van sterfte, indien van toepassing)

     Uiteindelik sal die vorms in die ART kliniek versamel word.

  2. **CMA nr (CM Audit nr):** Bel asb Dr K von Pressentin met ontslag/sterfte om ‘n Oudit nommer vir elke pasiënt te verkry. Hierdie CMA nr moet in plek van die leërnommer op alle data insamelingsvorms verskyn. Hierdie is noodsaaklik vir vertroulikheidsredes.

  3. **Pasiënt Register**

     Hou asb 'n data register in die sale, waar die pasiënt se oudit nommer (**CMA nr**), opname en ontslag datum en ART-kliniek datum ingevul kan word. Indien moontlik, faks/epos asb. ‘n kopie van die opgedateerde register elke maand aan my (faks: 023-626 1727).

  4. **Hou al die vorms in 'n leêr in die sale, sodat dit byderhand is as die pasiënt ontslaan word**.

Die waarde van die oudit proses kan tweeledig beskryf word:

1. *Review of clinical decision making and management*
2. *Making the most efficient use of resources for the patients*

(van "Medical audit: Rationale and practicalities" deur SP Frostick et al (editors))

Uiteindelik is die oudit proses die gevolg van 'n spanpoging om gelyke kwaliteitsorg aan alle pasiënte in die plaaslike gesondheidstelsel te bewerkstellig.

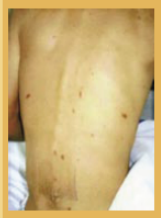
Kontak gerus die navorser, Dr Klaus von Pressentin, met enige navrae:

Tel: 023-626 8040; epos: klausvonp@gmail.com .

Guidelines for the Prevention, Diagnosis and Management of

Cryptococcal Meningitis

and Disseminated Cryptococcosis in HIV-infected patients



The diagnosis of cryptococcosis (CC)

- **Consider the diagnosis of CC if a patient presents with any of:** headache, unexplained fever, nausea and vomiting, neck stiffness, confusion, seizures, abnormal behaviour, new onset psychiatric symptoms, altered level of consciousness, focal neurological signs, diplopia, unexplained blindness or coma.
- Lumbar puncture is necessary for an aetiological diagnosis. If focal neurological signs are present, perform a CT brain (where available) to ensure LP is safe.
- **Recurrent CC:** Repeat LP must be done to confirm CC, to exclude concurrent pathology, to have an isolate for susceptibility testing and to identify and manage raised intracranial pressure.

Treatment of CC

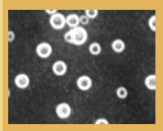
- **Antifungal treatment of a first episode of CC:**

Induction phase:	Amphotericin B 1mg/kg/dose ivi for 2 weeks (minimum 1 week)
Consolidation phase:	Fluconazole 400mg po daily for 8 weeks
Secondary prophylaxis:	Fluconazole 200mg po daily for life or until CD4>200cells/mm³ for more than 6 months on ART (at least 12 months fluconazole in total)

- **If fluconazole "resistance" suspected:** Fluconazole "resistance" may be present when CC recurs despite adequate initial treatment of CC and compliance with secondary prophylaxis

Induction phase:	Amphotericin B 1mg/kg/dose ivi for 2-4 weeks or until CSF is sterile
Consolidation phase:	Fluconazole 800mg po daily for 8 weeks with or without weekly amphotericin B 1mg/kg,
Secondary prophylaxis:	Fluconazole 400mg po daily OR Weekly amphotericin B 1mg/kg/dose OR Weekly amphotericin B 1mg/kg/dose plus 400mg fluconazole daily. Secondary prophylaxis can be discontinued if CD4 count is >200/mm³ for 6 months on ART(and at least 12 months fluconazole in total)

- **Management of raised intracranial pressure (>20 cm CSF)** Initially drain not more than 20-30ml of CSF. Repeat the LP to control intracranial pressure if pressure symptoms recur (headache, neck stiffness, altered level of consciousness, 6th cranial nerve palsy).
- **Pain and symptom management** Reduction of intracranial pressure alleviates headache and confusion. Residual pain may be managed with paracetamol and mild opiates Avoid non-steroidal anti-inflammatory drugs.



The role of the laboratory in the diagnosis and treatment of CC

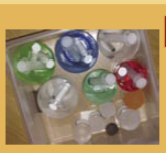
- **Cryptococcosis is diagnosed by culture of *Cryptococcus* species,** or a positive India ink test or a positive cryptococcal antigen detection test on any specimen or by histology.
- **Antifungal susceptibility testing for CC** Antifungal susceptibility testing (AFST) against fluconazole advised in recurrent or unresponsive cases where testing is available using Etest® (bioMérieux) or M27-A2 methodology. AFST is not recommended for amphotericin B.

DRUG INFORMATION: Amphotericin B

- **Dose and administration**
  - Prehydrate patients before every amphotericin B dose with 1 litre N/S containing 20mmol (1 ampoule) KCl.
  - Then administer amphotericin B 1mg/kg in 1l of 5% dextrose water in controlled infusion over four hours
- **Prevention and management of side effects**
  - Prevent nephrotoxicity and electrolyte abnormalities by:
    - prehydration,
    - avoiding nephrotoxic drugs (NSAIDs, aminoglycosides including streptomycin)
    - routine administration of oral potassium and magnesium supplements
  - Prevent phlebitis by rotation of the drip site every 2-3 days, and by flushing after infusion.
  - Prevent febrile reactions by administration of paracetamol 1g, 30 minutes prior to amphotericin infusion.
  - Monitor serum creatinine thrice weekly.
    - If serum creatinine increases by 2-fold or more, omit a dose of amphotericin B and/ or increase prehydration to 1 litre 8 hourly,
    - If serum creatinine fails to decrease after the above intervention, stop amphotericin B therapy and use fluconazole.

The role of antiretroviral therapy (ART) in patients with CC

- **Role of ART** ART naïve patients who develop CC should be treated with antifungal agents as above, and then commenced on ART as a matter of urgency. Commence ART 2-4 weeks after initiation of antifungal therapy.
- **Immune reconstitution inflammatory syndrome (IRIS)** IRIS may occur when a patient who has a history of adequately treated CC is started on ART and develops a recurrence of the meningitis. Management of a patient with suspected IRIS requires the following:
  - Continuation of ART
  - Repeat LP to exclude additional pathology, to obtain an isolate for susceptibility testing to fluconazole and to measure intra-cranial pressure.
  - Raised intracranial pressure should be treated with serial LPs
  - CT scan if focal neurology is present.
  - Appropriate antifungal therapy.
  - Culture-positive cases should receive treatment according to Recommendation 2.
  - Prednisone 1mg/kg daily for at least a week if symptoms fail to respond after appropriate management of raised intracranial pressure and symptomatic treatment. Some patients require prolonged courses of steroids.



CC in special populations

- **Cryptococcosis in pregnancy and women of childbearing age** No alterations in the management of cryptococcosis are required in pregnancy, due to high mortality associated with CC. Fluconazole is teratogenic; therefore women of child bearing potential who require fluconazole should use effective contraception.
- **Cryptococcosis in paediatric patients**

Antifungal treatment of CC in children

Induction phase:	Amphotericin B 1mg/kg/dose ivi for 2 weeks (relapse episodes should be treated for 4-8 weeks, preferably until CSF fungal culture is negative). Adequate hydration during amphotericin B treatment should be maintained.
Consolidation phase:	Fluconazole 12-15mg/kg once daily for a further 8 weeks (The maximum dose should not exceed 400mg)
Secondary prophylaxis:	Fluconazole 6-10mg/kg once daily for life. Secondary prophylaxis can be stopped in children over the age of 2 years who are asymptomatic with their last episode of cryptococcosis having been more than 12 months previously **and** who have evidence of sustained immune reconstitution on ART as follows: 2-6 years old: CD4 percent > 25%, more than 6 years old: CD4 count > 200 cells/mm³

- **Management of raised intra-cranial pressure in children** Recommendations for management of intracranial pressure in adults apply to children (i.e. repeated lumbar punctures).

For refractory raised intracranial pressure, referral to a specialist centre is advised.

Drug information, toxicities and interactions in patients treated for CC

Clinicians should be aware of overlapping toxicities particularly hepatotoxicity that occurs with the concurrent use of TB therapy (pyrazinamide, isoniazid and rifampicin) and nevirapine.

Fluconazole levels are reduced by concurrent rifampicin therapy. Clinicians may wish to increase doses of fluconazole when patients receive concurrent TB treatment

Supplementary management of CC

- **Counseling of patients diagnosed with CC**

All patients CC should be counseled (once fully conscious) regarding:

- The need for compliance with fluconazole therapy
- The urgent need for HIV testing (if HIV status unknown)
- Co-trimoxazole prophylaxis and ART if HIV positive

Contact Details: HIV CLINICIAN'S SOCIETY
Physical address:
Suite 150, 1st Floor, Dunkeld West Centre, 281 Jan Smuts Ave (cnr Bompas Rd), Dunkeld West, Johannesburg
Postal address:
Suite 233, Private Bag X2600, Postnet Killarney, Houghton, 2041
Tel: +27 (0) 11 341 0360 ext 287
Fax: +27 (0) 86 519 6247

Contact Details: GERMS-SA
Group for Enteric, Respiratory and Meningeal Disease Surveillance in South Africa
National surveillance for CC is performed by GERMS-SA. Contact the NICD (011-386-6000, www.nicd.ac.za) for information about the surveillance programme.

Design by Manik Design 011 482 3040

Addendum 6: CM Management Poster (SA HIV Clinician Society)

Addendum 7

Summary of the Pilot Audit results at Worcester Hospital, 2008

Comparing actual performance to the target standards

Criteria		***Level of Performance***	***Actual Performance***
Structure	Availability of Amphotericin B	100%	100%
	Availability of Fluconazole	100%	100%
	Protocol for the administration of Amphotericin B in ward	100%	**50%**
Process	Requesting CLAT on Indian ink-negative CSF samples	100%	100%
	Baseline U&E and biweekly U&E	100%	**92%**
	CT scan if depressed Level of Consciousness/Focal Neurology	100%	**75%**
	Use of CSF manometry in all LP's	100%	**23.1%**
	Completing target of 14 days of IV Amphotericin B	80%	77.8%
	High dose Fluconozole for 8 weeks (consolidation phase)	100%	100%
	Adherent to long-term Fluconazole (secondary prophylaxis)	80%	**71.4%**
	Referral to ART clinic	100%	100%
	Commencement of ART by week 4 into antifungal treatment	80%	**0%**
Outcome	Morbidity: incidence of drug-induced renal impairment (Amphotericin B)	20%	0 – 15% (i.e. <20%)
	2 month-survival post-diagnosis	60%	**46.2%**

Comparing actual performance to the target standards (continued)

Criteria	***Meeting Target Standard***	***NOT Meeting Target Standard***
Structure	Availability of Amphotericin B	Protocol for the administration of Amphotericin B in ward
	Availability of Fluconazole	
Process	Requesting CLAT on Indian ink-negative CSF samples	Baseline U&E and biweekly U&E
	Completing target of 14 days of IV Amphotericin B	CT scan if depressed Level of Consciousness/Focal Neurology
	High dose Fluconozole for 8 weeks (consolidation phase)	Use of CSF manometry in all LP's
	Referral to ART clinic	Adherent to long-term Fluconazole (secondary prophylaxis)
		Commencement of ART by week 4 into antifungal treatment
Outcome	Morbidity: incidence of drug-induced renal impairment (Amphotericin B)	2 month-survival post-diagnosis

Addendum 8

Communication with the Audit Team

An (unedited) example of an email sent to the audit team by the researcher (Audit Lead)

"28 Junie 2010

Aan: CM Audit Champions, Kaap Wynland Oos

Beste kollegas

Hoop dit gaan goed!

Ons is nou in die finale peilvlak van die CM oudit en die data-insameling periode eindig 30 Junie 2010.

Ek wil nou weereens jou (as "audit champion") hulp vra met die nagaan van die data insamelingsvorms deur op die volgende paar kwessies te let in die komende week:

1. Verseker asb dat alle data registrasie vorms bymekaar versamel word in die komende week.

2. Gaan asb die meegaande lys deur wat ons met die NHLS se hulp saamgestel het (alle positiewe CM toetse – dit onderskei ongelukkig nie tussen HIV positiewe en HIV-negatiewe gevalle nie; verder is die lys se periode langer as dié van die oudit: November 2009 – vandag, 28 Junie 2010). Trek asb die addisionele leêrs (indien nodig) en konsulteer asb met die ARV/infeksiekliniek om die data ivm ARVs in te samel.

3. Ek beplan om tussen 5-7 Julie die rondte te doen om by elk van die 5 "sites" te doen om die data vorms in te samel en om 'n kort onderhoud met julle te doen ivm jul ervaring van die oudit proses. Laat weet asb wanneer dit julle die beste sal pas – ek sal julle gedurende die komende week persoonlik bel om 'n tyd af te spreek!

Ek is baie dankbaar vir jul hulp tot dusver! Ek is ook opgewonde oor die data-lys vanaf die NHLS lab – ek wil asb die beroep op almal doen om deurgaans alle data en inligting as vertroulik te hanteer. Ek herinner julle ook aan die gees van nie-diskriminasie van die mediese oudit-proses/kwaliteitsverbeteringsiklus: geen hospitaal of individuele gesondheidswerker sal onregverdig gekritiseer word nie.

'The aims of this process are:

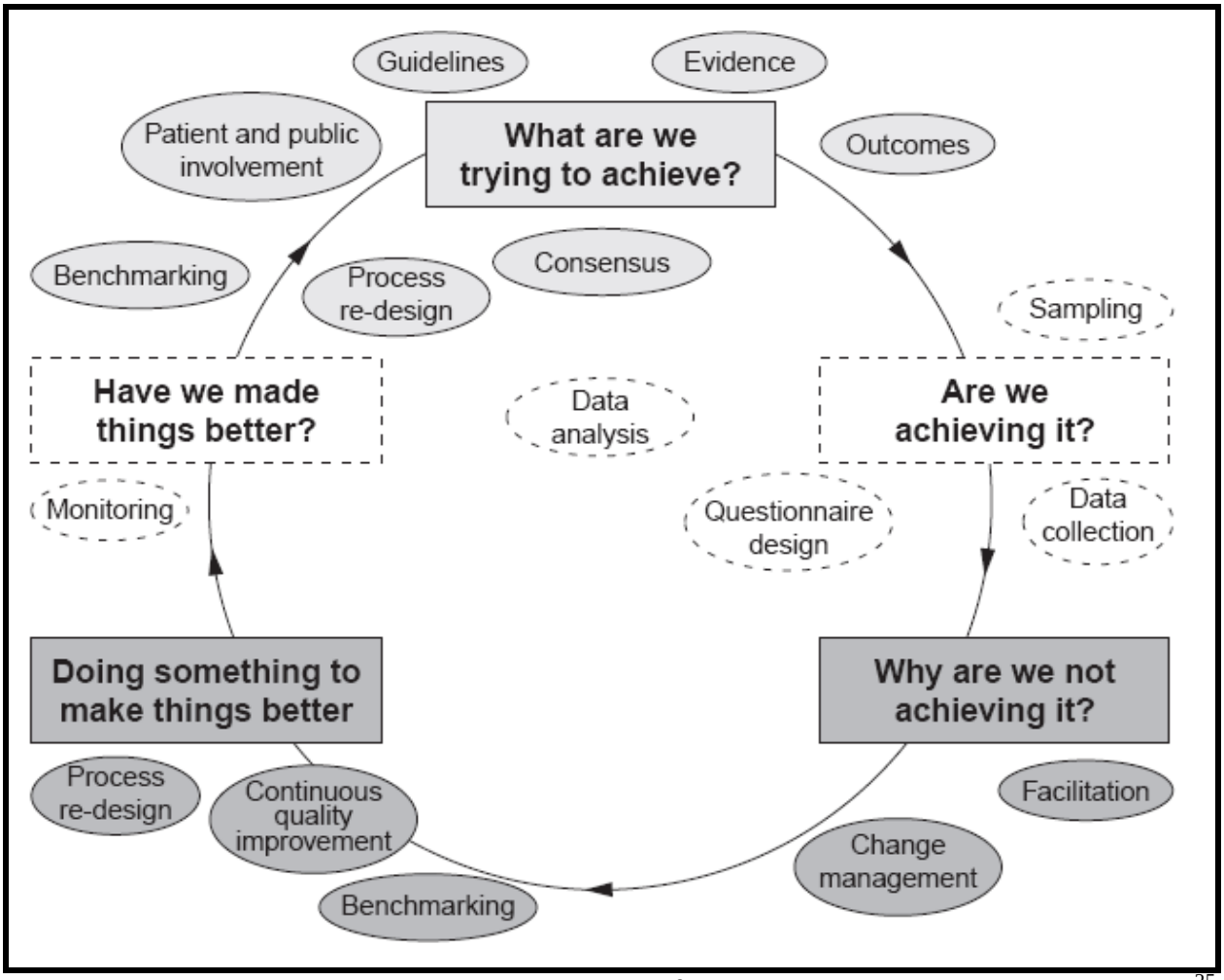
1. to audit the audit process: identifying pitfalls and challenges in the audit process in a multi-site audit, with special consideration of the challenges faced in the public health sector with limited resources (time, human resources, staff changeover, IT constraints, medical records)

2. to audit the management of CM, with consideration of challenges faced in the secondary vs. district hospital setup. (Medical audit: Rationale and practicalities)' [38]

Ek dink ons is besig met waardevolle werk – hierdie oudit en meegaande dinkskrum sal goeie voorstelle bied vir die distrik en sub-distrik besture, aangesien medies oudits deel is van die gesondheidsorg spektrum se toekoms, veral noudat konsepte soos "clinical governance, accountability and continuous quality improvement" alledaags raak. Die oudits itv chroniese siektes is 'n goeie voorbeeld van hierdie nuwe tendens.

Ek verwelkom julle terugvoer.
Groete, Klaus"

Addendum 9: Detailed Quality Improvement Cycle



NICE: Principles for Best Practice in Clinical Audit (2002) [25]

Addendum 10: Draft Document: Integrated Care Pathway

Draft document (Nr 1: August 2010)

Integrated Care Pathway

Management of Cryptococcal Meningitis in immune-suppressed Adults (Age > 13 years)

Cape Winelands (East) District
Western Cape, South Africa

This document should be completed for every patient diagnosed and admitted with Cryptococcal Meningitis at the following hospitals:

- Worcester hospital
- Brewelskloof hospital
- Ceres hospital
- Montagu hospital
- Robertson hospital

This document should be seen as a clinical record that is kept in the patient's folder.

All information should be kept confidential.

This is a guideline of best practice for the multidisciplinary team treating a patient admitted with Cryptococcal Meningitis. All actions/care must be signed for daily or a variance recorded if there is a deviance from the planned care. The pathway will be used for clinical audit purposes.

This document was prepared by Dr Klaus B von Pressentin, August 2010

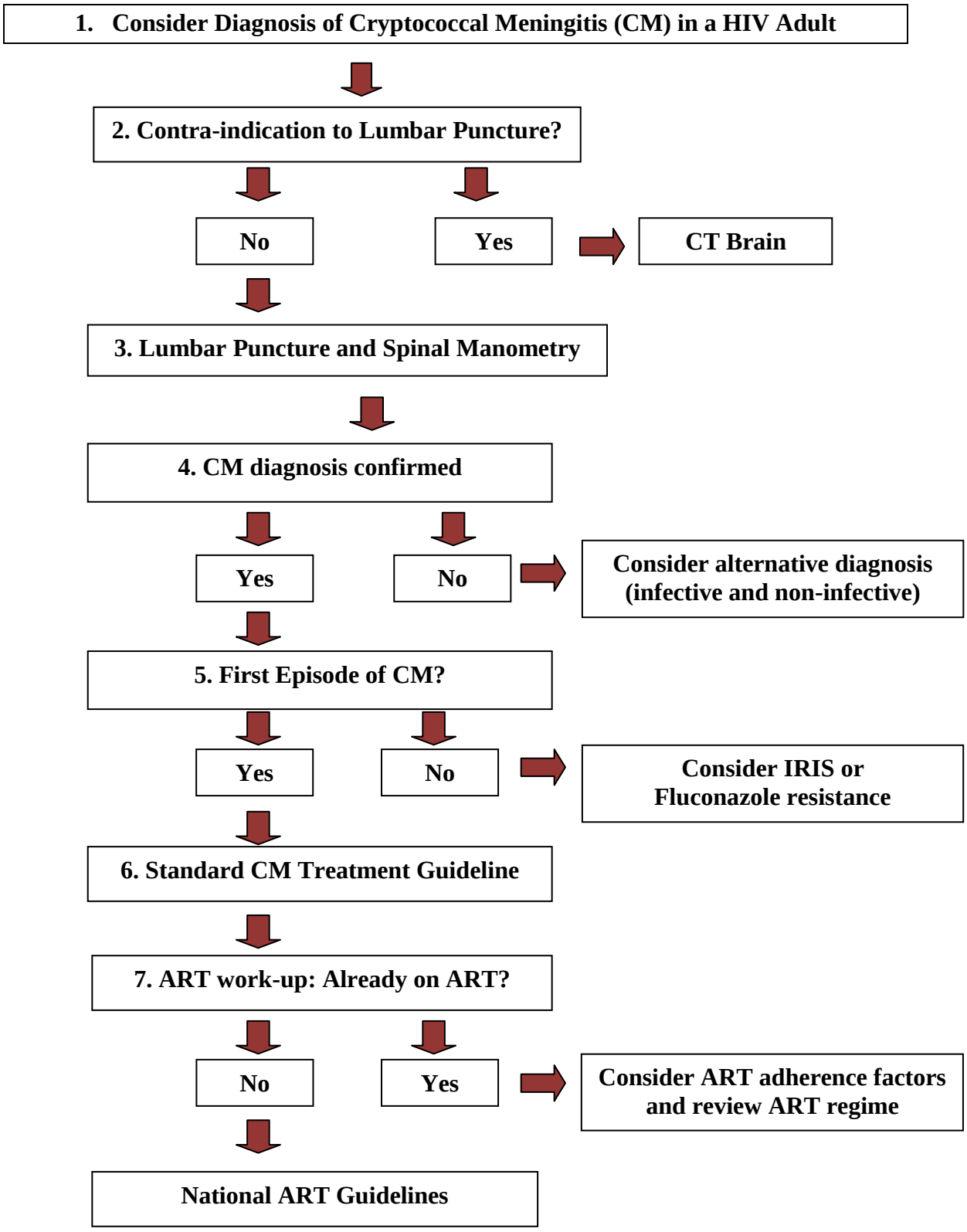
Admission Record

Hospital	
Ward	
Patient Name (use label if available)	
Patient Sex	
Folder Number	
Date of Birth / Age	
Address	
Date of Admission	
Date of Amphotericin B commencement	
Date of Discharge / Death	
Date of transfer to another hospital (if applicable; please document name of hospital and reason for transfer)	
Date of ART commencement	
ID clinic follow-up appointment date	
RVD status	
CD4 count	
Indian ink result	
CLAT result / titre	
Previous CM diagnosis?	

Evidence-base of Integrated Care Pathway

McCarthy K, Meintjes G, guideline writing committee. Guidelines for the prevention, diagnosis and management of Cryptococcal Meningitis and Disseminated Cryptococcosis in HIV-infected patients. S Afr J HIV Med. 2007;Spring:18-23.

Schematic overview of Integrated Care Pathway



Cryptococcal Meningitis Treatment Guidelines

1. Consider Diagnosis of Cryptococcal Meningitis (CM) in a HIV Adult

- headache
- unexplained fever
- nausea and vomiting
- neck stiffness
- confusion
- seizures
- abnormal behaviour
- new onset psychiatric symptoms
- altered level of consciousness
- focal neurological signs
- diplopia or unexplained blindness
- coma

2. Contra-indication to Lumbar Puncture?

If focal neurological signs are present, perform a CT brain (where available) to ensure LP is safe.

3. Lumbar Puncture and Spinal Manometry:

Document Opening Pressure and Volume CSF drained

Lumbar puncture is necessary for an etiological diagnosis.

Therapeutic tap if Opening Pressure > 20 cmH20:
Alleviate pressure initially by draining not more than 20 – 30 ml of CSF at initial LP
(to decrease Opening Pressure by 20 – 50%)

3.1 Request the following investigations routinely:

Microscopy (cell count, Gram stain and Indian ink stain),
Chemistry (protein, glucose), Bacterial culture (MCS);
Cryptococcal antigen (CLAT) detection should be requested only if the Indian ink test is negative

3.2 Consider the following investigations (in consultation with senior colleague):

Smear and culture for *Mycobacterium tuberculosis* (requires at least 5 ml CSF),
TPHA/VDRL for syphilitic meningitis, *Toxoplasma gondii* IgG and IgM.

4. Diagnostic Criteria for CM:
Positive Indian ink, or CLAT positive (titer > 1:8)

5. Treatment

First episode of CM

Induction Phase:
Amphotericin B treatment (1mg/kg)
for 2 weeks (minimum 1 week)

Consolidation Phase:
Fluconazole 400mg daily for 8 weeks

Secondary Prophylaxis:
Fluconazole 200mg daily for life
or until CD4 > 200 cells/mm^3 for more than 6 months on ART
(at least 12 months of Fluconazole in total)

Recurrent CM

Repeat LP must be done to

- confirm CM
- to exclude concurrent pathology
- to have an isolate for susceptibility testing
- and to identify and manage raised intracranial pressure

Antifungal Susceptibility Testing (AFST) against Fluconazole is only advised with recurrent CM.

In cases of suspected Fluconazole resistance or suspected CM IRIS, consult with the Specialist Physician at Worcester hospital or the Infectious Diseases specialist at Tygerberg hospital.

6.1 General treatment guidelines: Amphotericin B:

1. Dose used: 1mg/kg intravenous
2. Ampho B reconstituted in 1 liter 5% Dextrose water and administered over 4 hours
3. No test dose required if daily dose is run slowly over the first half hour of administration
4. Prevent Ampho B-associated renal impairment, hypokalemia and hypomagnesemia:
    a. Saline Preload Daily: 1 liter Normal Saline with 1 ampoule KCl (20 mmol) added, over 4 – 6 hours, prior to daily dose
    b. Avoid concurrent use of nephrotoxic medication (NSAIDs, Aminoglycocides)
    c. Monitoring of Creatinine, Potassium (K^+) and Magnesium (Mg^{++}): *see Calendar*
    d. If renal impairment occurs:
        i. If Creatinine increases by 2-fold or more, omit a dose and/or increase prehydration to 1 litre 8-hourly
        ii. If Creatinine fails to decrease after above intervention, stop Ampho B and use Fluconazole
5. Treat Ampho B-associated febrile reactions:
    a. Paracetamol 1g orally 30 minutes prior to dose
    b. Severe reactions may require hydrocortisone 25mg IV at the start of the infusion
6. Prevent Ampho B-associated thrombophlebitis:
    a. Flush line with 200ml Saline after each daily dose of Ampho B
    b. Change IV line every 2^{nd} – 3^{rd} day

6.2 General treatment guidelines: Fluconazole

1. Generally well tolerated
2. Beware of need to adjust dose according to GFR (glomerular filtration rate) and use in pregnant women (teratogenicity)
3. Beware of drug interactions (Fluconazole is an enzyme inhibitor: relevant with TB medication and Nevirapine)

Inpatient Treatment Calendar: Week 1

Induction Phase: <u>Week 1</u> of Amphotericin B treatment			Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Amphotericin B Treatment	Saline Preload Daily								
	Ampho B dose given Daily (if dose omitted, provide reason and action)								
	Document Febrile reaction (if present)								
	Saline Flush of Line after daily dose (200ml Saline)								
	Document drip line changed (change drip site every 2 to 3 days)								
	Creatinine, K^{+}, Mg^{++} twice a week (document values) (Days 1, 4, 7, 10, 13)								
	Weekly Ward Hb (Days 1, 7, 14)								
Spinal Manometry	Spinal Manometry (in cmH20, elevated if reading is >20 cmH20)	Opening Pressure							
		Volume drained (ml)							
		Closing Pressure (if possible)							
ART	ART counselling sessions								

Inpatient Treatment Calendar: Week 2

Induction Phase: Week 2 of Amphotericin B treatment			Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Amphotericin B Treatment	Saline Preload Daily								
	Ampho B dose given Daily (if dose omitted, provide reason and action)								
	Document Febrile reaction (if present)								
	Saline Flush of Line (200ml Saline after daily dose)								
	Document drip line changed (change drip site every 2 to 3 days)								
	Creatinine, K^{+}, Mg^{++} twice a week (document values) (Days 1, 4, 7, 10, 13)								
	Weekly Ward Hb (Days 1, 7, 14)								
Spinal Manometry	Spinal Manometry (in cmH20, elevated if reading is >20 cmH20)	Opening Pressure							
		Volume drained (ml)							
		Closing Pressure (if possible)							
ART	ART counselling sessions								

7. ART work-up

- All HIV-positive patients who develop CM are eligible for Cotrimoxazole prophylaxis
- Recommendation by SA HIV Clinician Society Guideline Committee:

  Start ART 2 – 4 weeks after onset of antifungal treatment (ART may be started as inpatient)
- Long in-patient stay is ideal for ART work-up and counselling
- ART work-up Blood tests as per national protocol: ALT, RPR, FBC & Diff
- ID clinic or local clinic appointment on discharge, to ensure seamless work-up and initiation of ART
- ID clinic or local clinic referral letter to be completed on discharge with other discharge documents

List of Abbreviations

Ampho B: Amphotericin B

ALT: Alanine transaminase

ART: Anti-retroviral Treatment

CLAT: Cryptococcal Latex Agglutination Test

CSF: Cerebrospinal Fluid

CT: Computer Tomography

FBC & Diff: Full Blood Count and Differential

GFR: glomerular filtration rate

Hb: Hemoglobin

ID clinic: Infectious Diseases clinic

IV: Intravenous

RPR: Rapid plasma reagin (test for syphilis)

RVD: Retroviral Disease (Human Immunodeficiency Virus)

U&E, Mg = Urea and Electrolytes, Magnesium