CLINICAL PRACTICE: POLICY

Routine cryptococcal antigen screening for HIV-infected patients with low CD4+ T-lymphocyte counts – time to implement in South Africa?

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Cryptococcal meningitis (CM) is a major cause of death among HIV-infected individuals. It causes an estimated 957 900 cases and 624 700 deaths worldwide annually, the vast majority of them in sub-Saharan Africa.[1] In Cape Town, CM is now the most common cause of adult meningitis (63% of all microbiologically confirmed cases[2]), and acute outcomes are poor.[3] Even with optimal treatment in study settings, 10-week mortality rates are between 24% and 37%.[4,5] In 2009, in a routine care setting at an urban hospital in Johannesburg, 67% of patients had died or were lost to follow-up at 3 months (N Govender *et al*., unpublished data). Unfortunately almost half of South African patients still receive sub-optimal initial treatment with oral fluconazole rather than intravenous amphotericin B.[3,6] Clearly, given the substantial mortality and morbidity associated with CM, preventive interventions should be prioritised.

As CM primarily affects patients with CD4+ T-cell counts ≤100 cells/μl, the incidence should fall during scale-up of antiretroviral therapy (ART) programmes, as in the high-income countries.[7] However, despite recent progress in expanding access to ART in South Africa,[8] the median CD4+ T-cell count of patients initiating ART remains low, and a high risk of new AIDS events and mortality persists during the first months of ART.[9] Numbers of CM cases in Cape Town remained constant between 2003 and 2008 despite a large increase in ART coverage,[10] and national surveillance shows slight increases in the incidence of reported CM cases year on year.[11]

With expanding ART access, an increasing proportion of CM diagnoses occur among patients already receiving ART – 20% in a cohort of CM patients from Cape Town.[12] Most of these patients had recently initiated ART (median duration 41 days), and their in-hospital mortality was high (29%).[12] CM is therefore a leading contributor to the high early mortality in African ART programmes. It accounts for up to 20% of all deaths,[9] many of which are thought to be due to 'unmasking' cryptococcal disease among patients who had sub-clinical disease when starting ART.[13,14]

To date, preventive strategies have consisted of routine fluconazole primary prophylaxis for all patients with low CD4+ T-cell counts. Although this approach reduces the incidence of CM,[15] concerns exist: fluconazole resistance may develop with widespread use;[16,17] it is not cost-effective;[18-21] it is teratogenic; and fluconazole has potential interactions with both ART and tuberculosis (TB) medication (Table I). These issues have led to very limited uptake of fluconazole primary prophylaxis in HIV treatment programmes.

Fortunately, research has demonstrated that nearly all patients at risk of developing CM during ART could be identified on entry into ART programmes by screening for sub-clinical infection using cheap (ZAR38.95), simple and highly sensitive cryptococcal antigen (CRAG) blood tests.[22] In 707 patients initiating ART in Cape Town, stored serum samples from 13% of patients with CD4+ T-cell counts ≤100 cells/μl tested positive for CRAG in a retrospective analysis. Prospective screening for CRAG in this cohort would have been 100% predictive of subsequent development of CM within the first year of treatment.[22] If identified prospectively, such patients could be given 'pre-emptive' treatment to prevent progression from cryptococcal antigenaemia to life-threatening meningitis. Such a 'targeted' prevention strategy would avoid many potential problems of widespread fluconazole use with a blanket primary prophylaxis approach.

Cape Town data also show that 73% of ART-naïve patients presenting with CM have already been diagnosed with HIV, a median of 4 months before CM, but developed disease before starting ART.[23] CRAG screening could also identify these patients, allowing for pre-emptive therapy and fast-tracking for rapid ART initiation – an issue of particular priority given the exceptionally high mortality of South African patients in this pre-treatment period.[24-26] If all patients who had previously tested HIV-positive (both those on ART and the 73% who were known to be HIV-positive but not on ART) had been screened, and effective interventions given, up to 78% of cases of CM could have been prevented.

CRAG screening directed at all newly diagnosed HIV-positive patients with CD4+ T-cell counts ≤100 cells/μl is likely to detect most cases. At a programmatic level, plasma from ethylenediaminetetra-acetic acid (EDTA) samples sent for CD4 count testing could

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Table I. Pros and potential cons of screening for serum CRAG among asymptomatic HIV-infected patients with CD4+ T-cell count ≤100 cells/μl

Pros	Cons
Cryptococcal meningitis is one of the most common HIV-related opportunistic infections in South Africa.	The optimal treatment of patients diagnosed with asymptomatic antigenaemia is not defined, **but** we can make recommendations pending further research.
If cryptococcosis is diagnosed when patients present with meningitis: • treatment is complex and expensive • requires 14 days admission • mortality is extremely high despite optimal treatment.	There are potential drug interactions between fluconazole and NNRTIs. Fluconazole increases nevirapine levels, **but** concomitant use has not been associated with increased nevirapine toxicity in the two published studies.[32,33]
The cost of a serum CRAG test is approximately R40 per test.	Fluconazole is potentially teratogenic, **but** pregnancy is uncommon among patients with very low CD4+ T-cell counts; this has not been reported as a problem where primary prophylaxis has been used. In an antigen screening programme, fluconazole exposure would be limited to patients at very high risk of developing life-threatening CM.
Screening asymptomatic patients and pre-emptively treating those with positive serum CRAG to prevent meningitis is cost-effective.	Fluconazole will increase pill burden, **but** is given once a day and is well tolerated.

automatically be tested for CRAG at the laboratory if the CD4+ T-cell count was ≤100 cells/μl for the first time in that individual, and in the future, development of point-of-care CRAG tests could allow testing at the clinic level, greatly simplifying the process.

The optimal treatment of asymptomatic CRAG-positive patients has not been studied. Natural history data from Cape Town suggest that ART alone is sufficient to clear asymptomatic antigenaemia in around 50% of cases.[22] However, the remaining 50% are at very high risk of developing symptomatic CM and death, so proactive management is needed. One approach would be to perform lumbar punctures for examination of cerebrospinal fluid on all antigenaemic patients to assess for CNS involvement. However, this may not be necessary among asymptomatic patients, would heavily burden an overstretched public health service, and would potentially render a screening programme unworkable. A more pragmatic strategy is to treat all asymptomatic antigenaemic patients with fluconazole according to dosing recommendations in national guidelines: 400 mg daily for 8 weeks followed by fluconazole 200 mg daily for at least 10 months (or until the CD4+ T-cell count rises to >200 cells/μl) and starting ART after the initial 2 weeks of fluconazole. Evidence that higher doses of fluconazole are more rapidly fungicidal[27] may change this dosing schedule in future to 800 mg daily for 8 weeks followed by 400 mg daily for at least 10 months. However, evidence to support empiric treatment of CRAG antigenaemia without CSF analysis is lacking, and studies are required. Whether CRAG titres could be used to stratify risk of progression to CM and guide treatment decisions and optimal timing of ART initiation in such patients must also be defined.

The reduction in morbidity and mortality, and the potential economic benefits of a screen-and-treat prevention strategy, are substantial.[28] In a cohort of South African patients starting ART, 31% of inpatient admission days within the first 32 weeks of ART were due to CM.[29] Each patient admission with CM is estimated to cost ZAR20 980 (at 2001 costing).[30] A cost-effectiveness analysis in Uganda, where CRAG testing costs four times more than in South Africa, suggested a cost of only US$190 for each case of CM prevented, and US$266 for each life saved.[31] Using data from a retrospective study of a South African cohort, 52 patients with CD4 counts <100 cells/μl initiating ART would have to be screened to prevent one case of CM.[22] At the current cost of ZAR39.85 (National Health Laboratory Service tariff), it would cost ZAR2 072 per case of CM prevented[22] – substantially less than the cost of hospital admission. But while evidence for the utility of CRAG screening to identify patients at risk of CM is compelling, key questions remain of how best to implement a screening policy and how to manage the asymptomatic CRAG-positive patients identified.

Further studies are planned to clarify these unresolved questions. However, we believe that the strength of the available evidence, coupled with the high ongoing mortality secondary to CM among South African HIV-positive patients, justifies implementation of CRAG screening in the South African HIV programme. This should involve a CRAG test on all patients diagnosed with HIV with a CD4+ T-cell count ≤100 cells/μl and treating all antigenaemic patients with fluconazole.

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MEDICINE AND THE LAW

The amended legislation on procedure-related deaths – an advance in patient care?

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Deaths during or after a surgical procedure may be considered medico-legal and subjected to medico-legal autopsy and inquest. We define death in medical terms and discuss the implications of the provisions of the Amended Health Professions Act of 1974 and its recent amendment. Problems with the old and new definitions of such deaths and whether the amendment provides additional patient protection for the patient are considered. We challenge the South African law-makers to review the all-inclusive terminology in relation to such deaths.

Introduction

Patients who undergo anaesthesia and medical procedures may die as a result thereof. South African law[1] requires any death considered unnatural[2] to be reported for medico-legal investigation. Unnatural death related to anaesthesia is provided for in the Health Professions Act.[3] In July 2008, a revised version of this statutory obligation came into effect with the proclamation of the Health Professions Amendment Act.[4] We examine the scope and significance of this amendment, and consider its implications for health care providers.

Background and definitions

The repealed law stated that 'the death of a person whilst under the influence of a general anaesthetic or local anaesthetic, or of which the administration of an anaesthetic has been a contributory cause, shall not be deemed to be a death from natural causes as contemplated in the Inquests Act 58 of 1959, or the Births, Marriages and Deaths Registration Act 81 of 1963'.[3]

The amendment provides that 'the death of a person undergoing, or as a result of a procedure of a therapeutic, diagnostic or palliative nature, or of which any aspect of such a procedure has been a contributory cause, shall not be deemed to be a death from natural causes as contemplated in the Inquests Act 58 of 1959, or the Births and Deaths Registration Act 51 of 1992'.[4]

Legislative protection for the anaesthetised patient appeared shortly after the introduction of anaesthesia to facilitate invasive surgical procedures.[5] The drug-induced state of deep unconsciousness and loss of voluntary faculties places patients in a position of vulnerability to hazards of the anaesthesia, and also in a totally compromised state where their lives are subject to the conduct of the health practitioners involved. The expectancy of death following procedures performed under anaesthesia varies widely, from 1 in 133 patients in Togo to 1 in 185 000 in the UK, raising concern about anaesthesia and peri-operative safety in developing countries.[6] The peri-operative death rate from inpatient surgery in industrialised countries is between 0.4% and 0.8%, and at least half of all surgical complications may be avoidable.[7] However, deaths caused by the anaesthetic procedure alone account for fewer deaths compared with the surgical procedure itself, with mortality associated with general anaesthesia alone ranging from 0.02%[8] reported in Finland, to 0.06%[9] reported as a global figure.

Issues pertinent to South Africa

The amendment in South African law appears to be related to the requirement for health professionals to recognise the need for greater protection for the vulnerable patient under their authority and care.[10] The wider-ranging provision in section 48 of the Health Professions Amendment Act permits legal inquiry into deaths which may have evaded investigation under the repealed section 56 of the Health Professions Act.

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