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ORIGINAL RESEARCH

CT before lumbar puncture in suspected meningitis in Botswana:
How established guidelines may not apply



*Tomodensitométrie avant ponction lombaire en cas de suspicion de méningite au Botswana:
Comment les directives classiques peuvent ne pas s'appliquer*

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Introduction: According to established guidelines from high-income countries, computed tomography of the head (CT) is indicated before lumbar puncture (LP) in the evaluation of suspected meningitis in HIV patients. In Botswana, meningitis in HIV-infected patients is common but CT is not widely available.

Objective: Develop a rational, evidence-based approach to CT use in the emergency evaluation of suspected meningitis in a population with high HIV prevalence.

Methods: Emergency center (EC) staff at Princess Marina Hospital in Gaborone, Botswana, reviewed indications for CT and LP in suspected meningitis. The authors considered existing evidence for CT before LP (mostly from high-income countries) and considered the epidemiology of central nervous system infections in Southern Africa. Draft guidelines were circulated to emergency center doctors and nurses, and to specialists in other hospital departments for review and comment before finalization.

Result: Available literature seems to indicate that in Botswana it would be possible to significantly limit the use of head CT before LP in HIV positive patients without increasing the incidence or risk of herniation. The guideline includes scenarios where an LP might be indicated in the presence of focal neurological findings and in the absence of a CT, in contradiction to established guidelines.

Discussion: The applicability of established guidelines for CT use in suspected meningitis is dependent on local epidemiology and resources.

Introduction: Selon les directives classiques provenant des pays à revenu élevé, la tomodensitométrie (TDM) de la tête est indiquée avant une ponction lombaire (PL) pour l'évaluation d'une possible méningite chez les patients infectés par le VIH. Au Botswana, la méningite chez les patients infectés par le VIH est courante mais la TDM n'est pas souvent disponible.

Objectif: Développer une approche rationnelle fondée sur des preuves relative à l'utilisation de la TDM en cas d'évaluation d'urgence d'une possible méningite au sein d'une population à forte prévalence du VIH.

Méthodes: Le personnel du Centre d'Urgences (CU) de l'hôpital Princess Marina à Gaborone, Botswana, a examiné des prescriptions de TDM et de PL en cas de suspicion de méningite. Les auteurs se sont penchés sur les cas existants de TDM avant PL (la plupart provenant de pays à revenus élevés) et ont examiné l'épidémiologie des infections du système nerveux central en Afrique australe. Des directives provisoires ont été distribuées à des médecins et des infirmières de centres d'urgences et à des spécialistes dans d'autres services hospitaliers pour examen et commentaires avant finalisation.

Résultat: Les publications disponibles semblent indiquer qu'au Botswana, il serait possible de limiter fortement l'utilisation de la TDM de la tête avant une PL chez les patients séropositifs sans augmenter l'incidence ou le risque d'engagement cérébral. La directive comprend des scénarios dans lesquels une PL pourrait être indiquée en présence de signes neurologiques focaux et en l'absence d'une TDM, contrairement à ce que préconisent les directives classiques.

Discussion: L'applicabilité des directives classiques relatives à l'utilisation de la TDM dans des cas de suspicion de méningite dépend de l'épidémiologie et des ressources locales.

African relevance

- A clinical guideline not practical in Sub-Saharan Africa can be adapted for local use.
- HIV-associated neurological infections are common in Africa.
- Emergency CT investigations are not feasible in much of Africa.

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Introduction

HIV prevalence in Botswana is 25% in the 15–49 year-old age group, and over 40% in the 40–44 age group.¹ Altered mental status, fever, neck stiffness, and focal neurologic signs are common clinical findings in patients presenting for emergency care in Botswana. The leading differential diagnosis for these clinical presentations is meningitis, a life-threatening emergency in HIV positive and negative patients alike. Diagnostic evaluation should proceed urgently and include a lumbar puncture (LP), which carries a low but non-negligible risk of brain herniation. Various authors have attempted to identify the minority of patients at higher risk of this complication.^{2–4} Well-established guidelines from high-income countries recommend computed tomography of the head (CT) to look for mass effect or hydrocephalus in patients meeting certain high-risk criterion prior to performing LP.⁵ In Botswana, patients with suspected meningitis commonly present with one or more high-risk criteria indicating CT. Criteria identified by Hasbun and others include immune-compromise (e.g., HIV), altered mental status, focal neurological deficits, age > 60, history of central nervous system disease, and seizure within the last week.⁶

Only the 2 largest referral hospitals in Botswana out of 26 hospitals in the public sector can perform a CT. Additionally, it is worth noting that a CT Head with contrast was typically only available during the daytime due to Radiology staffing limitations. During a significant portion of 2010 and 2011, malfunctions and subsequent repairs made CT unavailable at both referral hospitals. During those periods, emergency center (EC) patients were often transported to private hospitals for CT resulting in delays of up to 12 h to arrange transport, obtain the imaging, and await study interpretation. Transport of these patients required ambulances and emergency center staff, thus diverting resources away from current and potential EC patients. For remote hospitals without a CT, safe transport to a facility with CT presents an even greater challenge. Prolonged transport could reasonably be expected to contribute to poor outcomes in critically ill patients. A delay in appropriate antimicrobial therapy is associated with worsened outcomes for bacterial meningitis⁷ and in the setting of cryptococcal meningitis, a lumbar puncture is both diagnostic and life-saving.^{8,9} In high-income countries, CT may also delay time to antibiotics⁷ and evidence of CT overuse¹⁰ raises additional concerns in terms of resource utilization and cancer risk.¹¹

To our knowledge, no paper has reviewed the evidence and discussed the dilemma of performing LP for suspected meningitis when herniation risk factors are present and when CT is unavailable or potentially available with delays (from transportation, inter-facility coordination, etc.). We describe our evidence review process, and how, taking into account available resources and local epidemiology, we derived an evidenced-based guideline that supports proceeding directly to a lumbar puncture without performing a CT in select patients.

This paper does not include a formal quality of evidence review process, which is difficult, when little context-specific literature exists, and which may not always be realistic or applicable in LMICs.¹² This paper will also not discuss the consensus building options for guideline development, which have been extensively described elsewhere.¹³

Methods

All emergency medicine specialist physicians working at the Accident and Emergency Department (“EC”) at Princess Marina Hospital (PMH) in Gaborone, Botswana, collaborated to develop a guideline for the use of CT before LP in the evaluation of suspected meningitis. PMH is one of two tertiary referral centers in Botswana with CT. The specific issue of CT before LP was to be included in a broader guideline on the use of CT for non-traumatic emergencies. This guideline and others were part of a larger hospital-wide initiative to develop clinical guidelines for common conditions.

In the process of developing a guideline for rational use of head CT before LP in our setting, we reviewed the available evidence regarding the epidemiology of central nervous system (CNS) infections in Botswana and Sub-Saharan Africa, the herniation risk associated with LP in common CNS infections, and the ability of CT to predict herniation. Search terms for LP-associated herniation, using PubMed to search the MEDLINE database, include meningitis, herniation, lumbar puncture, and computed tomography/CT. Search terms for intracranial infections and lesions in Botswana and in Southern Africa as a whole included the following search terms in PubMed: Africa, Botswana, meningitis, HIV, toxoplasmosis, *Cryptococcus*, tuberculoma, tuberculous meningitis, neurocysticercosis, and central nervous system lymphoma.

After composing a first guideline draft, we solicited additional input from EC medical officers and nursing staff by presenting the draft at a departmental meeting. Additional feedback was incorporated into a penultimate draft in July 2011. Lastly, the draft was circulated by e-mail and in person to the heads (and/or their designees) of those departments at PMH deemed to have the greatest stake in the guideline. Input was received and incorporated into the guideline until December 2011, with representation from the specialties of medicine, pediatrics, adult and pediatric infectious diseases, and radiology.

Result

We developed decision rules concerning the performance of CT before LP, which were acceptable to the departments concerned, notably the EC, Radiology, and the most frequently admitting departments, Medicine and Pediatrics (Box 1).

Box 1 Guideline for rational use of head CT before LP.

Indications for Emergency Head CT (all hours)

- Suspected Severe CNS infection with coma (GCS \leq 8) and/or posturing.
 - Rationale: Evaluate for mass effect, obstructive hydrocephalus, edema.
 - Note: if suspect cryptococcal meningitis, consider LP before CT.

Indications for semi-emergent head CTs (daytime, as these may require contrast)

- New onset seizures (regardless of immune status).
- Suspected CNS mass/SOL (Space-Occupying Lesion) (regardless of immune status).
- Unexplained altered mental status not covered above (regardless of immune status).
 - Not clearly caused by hypoxia, hypotension, hypoglycemia, etc.
- Suspected moderate CNS infection with confusion or focal neurologic findings.
 - If after-hours, do not wait for CT to do careful LP for possible crypto or TB meningitis.

The following are NOT indications for emergency head CTs

- Suspected meningitis if no confusion or focal neurological findings (go straight to LP).

Additional Notes

- TB meningitis (TBM): May cause CVA. TBM and CVA may occur together.
- Children are at higher risk for brain herniation. Those with risk factors for herniation, including GCS $<$ 8 should have their LP deferred and start antibiotics immediately.
- LP before CT in HIV+ adults: expert consensus in Botswana, where cryptococcal and TB meningitis are common, but toxoplasmosis is rare, suggested cautious LP first if CT is not immediately available.

Review of the available literature suggested that in Botswana it would be possible to significantly limit the use of head CT before LP in HIV-infected adult patients without increasing the incidence or risk of herniation (Table 1).

In weighing the risk of benefits of LP in adults related to prevalent conditions in Botswana, in most cases a cautious LP without CT was preferable to a greatly delayed LP after CT. However, in the event that CT was available within 1–2 h, we favored CT before LP in the presence of confusion or focal neurological deficits. A “cautious” LP was understood to be one in which the practitioner was aware of the potential risk of herniation, and one in which the practitioner removed the minimum fluid for diagnosis (barring cases of presumptive cryptococcal meningitis.) In the presence of normal neurological examination, HIV infection alone was not considered an indication for CT before LP in suspected meningitis.

Again weighing the risks and benefits for pediatric patients, we deemed that most children with a non-focal neurological examination and with a normal to slightly depressed level of consciousness did not need a CT and could safely undergo LP. Those with high-risk neurological findings (seizures, posturing, pupillary abnormalities, focal neurologic findings, GCS $<$ 12) should have their LP deferred and antibiotics initiated, whether or not CT is available. Since CT is unlikely to influence the immediate management, CT, like LP, could also be performed in a delayed fashion depending on availability and clinical progression.

Discussion

This guideline outlines the indications for safely performing a lumbar puncture without a CT scan in patients with suspected meningitis, which differ from standard practice in high-income countries. The suggested approach finds support in a review of relevant literature and of regional epidemiology, with consideration for the availability of CT. Groups in other LMICs, notably in South Africa, have made similar recommendations to proceed to LP without CT in defined circumstances.^{14–16}

Herniation risk as determined by CT

Evidence suggests that a normal CT does not rule out the risk of herniation and that herniation may occur in meningitis even when a lumbar puncture is withheld.^{2–4,17,18} Although LPs have been safely performed in patients with mass effect,^{19,20} most experts nevertheless agree that findings of mass effect or impending herniation on a CT constitute clear contraindications to LP.

Epidemiology of HIV and intracranial infections in Botswana

The Infectious Disease Society of America (IDSA) Guidelines for Bacterial Meningitis⁵ reference and incorporate Hasbun’s evaluation of clinical risk factors for CT head abnormalities that would contra-indicate an LP in suspected meningitis.⁶ In Botswana, immunosuppression from HIV was the most common high-risk criteria that would indicate the need for CT before LP. Altered mental-status and focal neurologic findings also occurred with high frequency in HIV patients presenting with suspected meningitis. The HIV prevalence among patients admitted to the adult medical wards in PMH ranges between 50% and 66% (Michelle Haas, Botswana-UPenn Partnership, personal communication, 2012). One American study found that a CD4 count $>$ 200 cells/ μ L greatly decreased the risk of an abnormal finding concerning focal brain lesions (FBLs) on CT.²¹ However, patients presenting to the EC at our referral center are often unaware of their CD4 count. Furthermore, a CD4 cut-off of 200 cells/ μ L might be less useful in Botswana, where brain tuberculomas occur at CD4 counts $>$ 200 cells/ μ L. Additional CNS pathologies associated with mass effect and/or potential herniation risk in HIV/AIDS patients include toxoplasmosis, primary central nervous system lymphoma (PCNSL), brain abscess, and non-communicating hydrocephalus in *Mycobacterium tuberculosis* (TB) meningitis.

Table 1 Aetiologies and relative frequency of meningitis and infectious focal brain lesions or hydrocephalus.

	Botswana		Southern Africa	
	Meningitis/encephalitis	Focal brain lesions	Meningitis/encephalitis	Focal brain lesions
Children*	48 Deaths 2008 ²² 63% Unspecified M 19% ABM 10% Encephalitis 6% Crypto 2% TBM CSF: ²⁵ 89% Culture neg. 11% Culture pos. • 82% Bacterial M o (95% If age < 5) • 18% Crypto 4 (5% If age < 5) • 0% TB	0 Deaths 2008 ²²	57–99% Hydrocephalus in TBM, of which 25% non-communicating ⁴⁷	13% of TBM cases have TB FBL ⁴⁷
Adults	405 Deaths 2008 ²² 35% Crypto 34% Unspecified M 10% ABM 9% TBM 9% Encephalitis 2% Viral Meningitis CSF: ^{25,26} 76% culture neg. • 61% lymphocytic • 24% culture pos. • 86% Crypto • 11% ABM • 4% TBM	6 Deaths 2008 ²² 1 Toxo 4 Abscess or granuloma 1 TB FBL 1% Of all deaths from CNS infections No PCNSL or NCC cases reported	21–63% Crypto 12–36% TB 8–31% ABM ^{30–33} 40–50% Hydrocephalus in TBM ^{27–29}	11–53% TB FBL 3–38% Toxo 0–19% NCC 0–13% Abscess 0–3% PCNSL ^{34,37} TB FBL 3.5–4.5 X less common than TBM ^{32,33}

* Deaths reported in Botswana's Health Statistics Report use age ≤ 14 as the definition for children and exclude neonates, while the studies reporting CSF pathogens in Botswana use age ≤ 12 and include neonates; M, meningitis; FBL, focal brain lesion; CSF, cerebrospinal fluid; TBM, tuberculous meningitis; TB FBL, tuberculoma; ABM, Acute bacterial meningitis; Crypto, cryptococcal meningitis; Toxo, toxoplasmosis; NCC, neurocysticercosis; PCNSL, Primary Central Nervous System Lymphoma.

In Botswana, meningitis appears to be more common than FBLs. Although it must be taken in the context of lack of widespread availability of CT, the Health Statistics Report 2008²² counts only 6 deaths related to FBLs (toxoplasmosis, abscesses, TB FBL, and granulomas, the majority of the latter likely due to TB) compared to 453 deaths from meningitis and encephalitis. Of the meningitis and encephalitis deaths, leading individual causes were “meningitis, unspecified” (36%), *Cryptococcus* (32%), “bacterial meningitis, unspecified” (10%) TB meningitis (8%), and “encephalitis, myelitis and encephalomyelitis, unspecified” (8%). Table 1 presents the same data for adults and children separately. As corroborating evidence for the low incidence of toxoplasmosis encephalitis in Botswana, the prevalence of antibodies to *Toxoplasma* was only 6.5% in one HIV-infected study population.²³ The Health Statistics Report 2008 does not contain any specific references to PCNSL. The paucity of PCNSL seen in clinical experience was later confirmed by a review of over 300 cancer cases at PMH, which did not contain a single case of PCNSL (Scott Dryden-Peterson, Botswana-Harvard Partnership, personal communication 2012). Case series of autopsies in adults and children performed in HIV patients before the availability of anti-retroviral therapy also point to a predominant burden of meningitis over FBLs.²⁴

In Botswana, *Cryptococcus neoformans* causes the greatest proportion of meningitis in adults, whereas bacterial

pathogens constitute the majority of meningitis cases in children. TB likely follows second for both adults and children in Botswana where TB incidence is estimated at 550/100,000. In a review of 7501 cerebrospinal fluid (CSF) analyses from 2000 to 2008 at PMH showed *Cryptococcus* in 85% of culture positive samples in adults (defined as age ≥ 13).²⁵ In children under 5 in same study, bacterial pathogens accounted for greater than 95% of all culture positive cases. It is worth noting, that no pathogen was identified in 79% of samples. It is likely that the 4% TB meningitis reported in adults is a gross underestimate: Another study of CSF samples at PMH also found that 61% of culture negative samples had a lymphocyte predominance and > 20 cells/ μ l, at a time that CSF mycobacterial culture was unavailable.²⁶ To our knowledge, there is no data on the frequency of hydrocephalus in association with TB meningitis in Botswana. Published studies suggest 40–50% of adults with TB meningitis will have hydrocephalus, the majority of which will be communicating and therefore not a herniation risk.^{27–29}

Epidemiology of intracranial infections in Southern Africa

Given the incomplete evidence on the etiology of intracranial infections in Botswana, we reviewed regional data from countries with similar HIV prevalence. In a Zimbabwean study of

meningitis etiology, *Cryptococcus* was identified in 45% of cases, pyogenic meningitis in 16%, and TB in 12%.³⁰ In a South African study population, *Cryptococcus* caused 63% of adult meningitis cases with a microbiological diagnosis, followed by TB (27%), and bacterial meningitis (8%).³¹ Though TB meningitis appears to be much more common than tuberculoma,^{32,33} tuberculomas seem to be the most common cause of FBLs, with some regional variation. In a review of 32 patients with HIV and FBLs from Gauteng, a region of South Africa with geographic proximity and similarity to Botswana, tuberculomas constituted the leading diagnosis, followed by neurocysticercosis as a distant second.³⁴ In the same series, there was only 1 presumed diagnosis of PCNSL and 2 presumed diagnoses of toxoplasmosis, in a region with a low reported toxoplasma antibody prevalence of between 6% and 10%,^{35,36} which is similar to rates reported in Botswana. In a contrasting case series of 45 patients from the wetter, more tropical KwaZulu Natal province of South Africa, where the toxoplasma antibody prevalence may be as high as 46%, toxoplasmosis accounted for the greatest share of FBLs, followed by brain abscess and tuberculoma with once again, a notable absence of PCNSL diagnoses.³⁷ PCNSL appears to be relatively uncommon in Sub-Saharan Africa, with similar data reported in South Africa, Zimbabwe, Tanzania, and Nigeria.^{38–41} Neurocysticercosis occurs relatively frequently in the region.⁴² There have been no reported human cases in Botswana although neurocysticercosis is considered to be endemic in the country,⁴³ and the disease has been reported in pigs.⁴⁴

Additional considerations for adult recommendations

We considered the overall risks and benefits of a lumbar puncture, with or without CT. In the case of cryptococcal meningitis, the most common kind of meningitis in adults in Botswana, it is widely recognized that prompt recognition and management of elevated intracranial pressure by serial lumbar punctures is a cornerstone of treatment.^{8,9} The IDSA guidelines recommend a CT before LP in patients with focal findings or depressed consciousness. However, in HIV positive patients with cryptococcal meningitis, most CT scans do not reveal contraindications to lumbar puncture, even in the presence of focal neurologic findings.⁹ Focal neurological findings also frequently occur in TB meningitis due to vasculitis-related infarction, without any mass effect or hydrocephalus.^{27–29,45–47} Additionally, LP has been described in the treatment of TB meningitis with communicating hydrocephalus,²⁹ and as a diagnostic method to distinguish communicating from non-communicating hydrocephalus with no reported post-LP herniation.⁴⁵ Furthermore, CT imaging has not been shown to be effective in distinguishing the two types of hydrocephalus.⁴⁶ In the case of other types of meningitis, the lumbar puncture may not be of immediate clinical benefit, but the fluid analysis will likely contribute useful clinical information within one to two days. Herniation shortly after lumbar puncture has been described in adults with bacterial meningitis in the setting of a normal CT, though these patients typically have signs of elevated intracranial pressure.⁴

In summary, non-communicating hydrocephalus and FBLs appear to be uncommon in adults in Botswana. The most frequent FBL is tuberculoma, occurring with much lesser frequency than TB meningitis. As some indication of an

additional margin of safety, case series of HIV positive patients with known FBLs or non-communicating hydrocephalus have described the performance of LP for diagnostic purposes without reporting complications.^{19,34,45}

Additional considerations for pediatric recommendations

We decided that pediatric patients (defined as age ≤ 12 at PMH) deserve separate consideration. HIV prevalence in this age group is between 2.2% and 4.7% (2008 BAIS), and therefore considerably lower than that of the adult population. The 2008 Health Statistics Report provides further evidence that classic HIV-related opportunistic infections constitute only a small portion of the CNS infections in children: of 1074 inpatient pediatric deaths, 30 were from “unspecified meningitis”, 9 from bacterial meningitis, 3 from cryptococcal meningitis, and 1 from TB meningitis.²² No deaths were reported from toxoplasmosis or intracranial abscesses. Published data from PMH supports that the majority of culture positive pediatric specimens were bacterial with relatively few cryptococcal cases.²⁵ Reports regionally have found very high TB meningitis incidence rates in children and TB incidence in Botswana is high, therefore it is likely that there is significant under-diagnosis of TB meningitis in Botswana.⁴⁸

Hydrocephalus frequently occurs in pediatric TB meningitis, with 57–99% rates reported depending on the series.⁴⁷ In a large series from a teaching hospital in Cape Town, 25% of children with TB meningitis had non-communicating hydrocephalus, the type associated with a herniation risk.⁴⁷ It is worth noting that all patients in this series had a lumbar puncture, without specific mention of herniation resulting from the procedure.

Given the relative dominance of bacterial meningitis in pediatric CNS infections, and the paucity of cryptococcal meningitis diagnosed in children, we focused on the risk of herniation in bacterial meningitis. A series of bacterial meningitis cases in children from Nigeria reports an 18% herniation rate, with almost one half occurring after lumbar puncture.⁴⁹ Expert reviews of the topic seem to concur that a normal CT and normal optic disks do not predict an LP free of herniation risk, while certain clinical signs, such as seizures, posturing, pupillary abnormalities, and GCS < 12 significantly increase the risk of herniation.^{2–4}

Next steps

The completed guideline was disseminated to the EC staff according to the PMH’s established guideline implementation process. The guideline was also shared with members of the National Guideline Committee, in the hope the PMH guideline could be harmonized with the next draft of the guideline on the diagnosis and treatment of meningitis. Since the PMH guideline recommendations include scenarios when CT is not easily available, it is anticipated they will be easily applied in primary and secondary hospitals as well as in referral centers.

Conclusion

In Botswana, limited resources and local epidemiology affect the applicability of international guidelines on the use of CT

before LP in suspected meningitis. A careful review of the literature allows for an evidence-based adaptation of guidelines to suit local realities. The process of reviewing regional epidemiology is likely to be generalizable to other regions of the world, and likely to inform others' efforts to develop guidelines that are context specific and evidence based. Further research is needed to study the dissemination of and adherence to the guidelines, and to monitor the clinical outcomes related to their recommendations.

Conflicts of interest

The authors declare no conflict of interest.

Author contributions

Guideline Development: Kestler, Caruso, Chandra, Goldfarb, Haas. Article Drafting: Kestler, Haas. Critical Revision & Final Version Review: Kestler, Caruso, Chandra, Goldfarb, Haas.

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