



Meningitis as a major contributing factor to mortality

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Provenance: This is an invited article commissioned by the Section Editor Dr. Mi Zhou (Children's Hospital of Soochow University, Soochow, China).

Comment on: Tenforde MW, Mokomane M, Leeme TB, *et al.* Mortality in adult patients with culture-positive and culture-negative meningitis in the Botswana national meningitis survey: a prevalent cohort study. *Lancet Infect Dis* 2019;19:740-9.

Received: 29 September 2019; Accepted: 30 October 2019; Published: 31 December 2019.

doi: 10.21037/arh.2019.10.03

View this article at: <http://dx.doi.org/10.21037/arh.2019.10.03>

Meningitis continues to be a leading cause of mortality, especially in regions with high prevalence of HIV (1). Although their main objective was to address predictors of mortality in a community in sub-Saharan Africa with high prevalence of HIV, Tenforde and colleagues' retrospective study also draws attention to this continued gap in care for patients in these settings (2). The study surveys retrospectively both culture positive and culture negative meningitis and provides the CSF parameters of 3,186 adult patients and their correlation with mortality. In their report, almost half of all patients evaluated died within 1 year of lumbar puncture (LP) despite 2,900 of the 3,186 patients having negative cultures.

The data for the study was collected over 11 years via two separate nationwide databases: the Botswana national meningitis survey, which had all CSF records of patients who had received LPs as well as the national electronic medical record, the Integrated Patient Management System (IPMS). A total of 29,704 patients 16 years of age or older were originally pulled from the IPMS before inclusion criteria was applied leaving them with 19,409. While the specific criteria were used to include patients, there was a random selection of 2,000 patients with negative CSF cultures. Knowing the prevalence of HIV was high in the community they were surveying (25% based on the national HIV registry), and that mild pleocytosis is seen in this population, they chose to include both individuals with normal CSF white blood cell (WBC) count (0–2 cells per μL) and with mild elevation (3–20 cells per μL) as half of the randomly selected patient group ($n=1,000$) and included the other half of the culture negative patients as those with

elevated CSF WBC count greater than 20 cells per μL .

The study identifies, as expected, pneumococcus was shown to be associated with the highest WBC count (median 236 cells per μL), highest protein (4.14 g/dL), lowest glucose (0.04 mmol/L) and the 2 and 10 weeks mortality was 44.1% and 47.1% respectively. The 1-year mortality was very high whether or not an organisms were identified (pneumococcus, 49.2%, tuberculous, 56.3%, and no pathogen identified, 48.4% and 48.7% in low WBC and high WBC counts, respectively). Seventy-three of the patients with culture negative meningitis had documented HIV infection, and of these 45% were on anti-retroviral therapy (ART) by the date of the LP. Patients in whom HIV status was unknown had a higher mortality, for example, those in the pneumococcal group 44/123 patients had unknown HIV status and had a 1-year mortality of 82%. It was recognized that this could be a reflection of survival bias where patients with undiagnosed HIV infection would die before their diagnosis could be made. Cryptococcus, as expected, was significant in this HIV population, and identified as the most common microbiological diagnosis (82%) and had the lowest percent survival over at 1 year. TB testing was rare with culture done in 9% of all samples collected.

The study did have limitations which the authors identified most notably being the lack of information surrounding the clinical presentation. Also, no information of the impressions of the physician's in care of the patients was available and no information of which, if any, antimicrobials the patient was treated with was available, to better understand if, in the absence of testing, empiric

therapies were provided. Finally, it was unclear how meningitis was defined, e.g., if some of the 888 pts with 0–2 CSF WBCs have normal CSF glucose and protein (no meningeal inflammation and normal parameters), then those patients do not fit definition of meningitis if no pathogens were identified and therefore should not be included in such a study.

The discussion does include other potential infectious etiologies, but it remains unclear whether any of these conditions were evaluated for. Herpes simplex infection has a clear link with HIV acquisition (3,4). Unfortunately, the global burden of disease is still unknown, however community specific studies have been performed. In South Africa, a neighboring country of Botswana, a survey of patients with symptomatic genital ulcer disease found that 60.7% of 771 patients with genital ulcer disease tested PCR positive for HSV and the seroprevalence of HSV-2 was 80.2%. Sixty-eight percent of patients who tested positive for HSV were found to be co-infected with HIV in this study (3). Information regarding testing of CSF with HSV PCR, could be helpful, but considering the cost of the test, it may not have been available (5-7), therefore it would have been helpful to know patients who were tested for HSV, and if not tested treated empirically with acyclovir, given the large number of culture negative CSF results with evidence of pleocytosis (average lymphocyte count was 88% in this group). At the same time, cited in the paper is a prospective cohort study of HIV-infected adult patients in Uganda presenting with suspected meningitis, where of 314 patients who were tested, 60% resulted positive for *Cryptococcus*. One hundred seventeen patients with either known *Cryptococcal* meningitis were also tested for viral pathogens and none of these returned positive for HSV. Therefore, the lack of this data may not necessarily be a major limitation to this study.

Information regarding the clinical presentation and management were also highlighted as limitations in this paper. Timing to initiation of antibiotics and head imaging may could have been beneficial information to the reader. Initiation of antibiotics prior to LP may have sterilized the CSF and could be an explanation of the high number of patients with abnormal indices but negative CSF culture. Antibiotics may have been provided before LP if CT imaging was performed to rule out mass effects and risk of herniation. In addition to this, any reason for delay in antibiotics would also be important to know. It has been studied that delay in antibiotic initiation by more than 3 hours is associated with poorer outcome in pneumococcal

meningitis, and more than 4 hours for community acquired meningitis (8,9). Suspicion or discovery of noninfectious etiologies also may alter the findings as symptoms leading to the LP and clinical judgement are not available. It is clearly stated that the authors assumed the CSF studies were obtained for suspicion of meningitis however note that some could have been obtained for evaluation of cancer, autoimmune disorders and other noninfectious work up.

TB meningitis and pneumococcal meningitis had very high mortality rates in this HIV positive population and the paper illustrates a final important point of the benefits of early diagnostics in this resource limited community. Most notably, they discuss the possibility of undiagnosed cryptococcal meningitis and tuberculous meningitis. In regard to *Cryptococcus*, mortality rate is 100% within 2 weeks without appropriate diagnosis and treatment (10). *Cryptococcal* antigen testing was reported to not have been performed frequently. The lateral flow assay which has high sensitivity [99.3% sensitivity and 99.1% specificity (11)], unfortunately was not available during this study. Although India Ink testing, as reported in the paper, could pick up most cases (sensitivity 86%) (11), it still could miss a large enough number of patients to have contributed to the culture negative patient pool that did poorly. Unfortunately, the number of patients started on anti-fungal regimens empirically is also not known although this could have impacted the resultant data. Same could be mentioned for Tuberculosis; testing was rare, with culture done in 9% of patients and AFB microscopy on 13%. Tuberculous meningitis can have a varying inflammatory picture, from acellular, to lymphocytic and neutrophilic predominant CSF. This diagnosis could also be a possible explanation for the high number of culture negative cases in general and for the high mortality within this group. Considering how highly prevalent TB is in this community, more sensitive testing including second generation Xpert MTB/RIF testing (Xpert Ultra) would be a benefit as it may yield high positive results for TB compared to culture, which is volume dependent (12).

Diagnostics in resource-limited countries continue to be a limiting factor in optimal treatment of infectious disease. Identification of pathogens leading to high mortality is critical in any patient setting, especially in resource-depleted countries such as Botswana and especially among immunodeficient patients such as those with HIV. The authors of this paper supported this with the data gathered. Increasing the access to diagnostic tools in such areas may impact the morbidity and mortality of these patients.

While culture is the gold standard for diagnosis of bacterial meningitis polymerase chain reaction (PCR) is available for many viral, fungal and bacterial pathogens, has a quick turn around and could help to distinguish Gram stain and culture negative CSF as bacterial meningitis when there is strong clinical concern. Multiplex assays have the benefit of evaluating many organisms on one test by using multiple primers to target DNA of various organisms on one assay (13). Multiplex PCR has been successfully introduced in resource poor countries although the impact on factors such as antibiotic usage is not yet clear (14). Although PCR is highly sensitive for detection of organisms it can be relatively expensive, and so other options such as antigen detection may have a role in resource poor settings. The Pneumococcal antigen test, though originally studied in urine, has been found to have a sensitivity and specificity of 95–100% and 100%, respectively in CSF (15). Limitations to this method of diagnosis would be lack of antigen testing available for many common pathogens. As implication of additional diagnostics occur, future directions could be to perform cost-analyses in the community and compare the impact of these new testing to the cost of care for the patient without a clear diagnosis. In addition to this, re-evaluation of the mortality after introduction of diagnostic testing mentioned above may shine light on this continued need and may help benefit other communities questioning the utility of initiating these studies.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/arh.2019.10.03

Cite this article as: Akindele NP, Kim KS. Meningitis as a major contributing factor to mortality. *Ann Res Hosp* 2019;3:17.