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# Treatment of tuberculous meningitis: Overdue for concerted action

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Notwithstanding the now ~50 year old advent of effective combination chemotherapy for pulmonary tuberculosis (PTB), tuberculous meningitis (TBM) still kills approximately 25% of those affected and significantly disables a further 25% of survivors [1,2]. Antibiotic drug regimens for TBM are based on those for PTB and do not account for the decreased penetration, in particular of rifampicin, into the central nervous system (CNS) [3]. It is also widely acknowledged that the tissue-damaging host inflammatory contribution to pathology is marked in TBM. Yet only adjunctive corticosteroid therapy in HIV-1 uninfected TBM patients reduces mortality, although not long-term disability [4,5].

It is welcome therefore that Sahib and colleagues report a trial of an intensified antibiotic regimen for TBM [6]. Linezolid is an effective antitubercular used in regimens to treat drug resistant TB and achieves relatively high cerebrospinal fluid (CSF) exposures. In the study, 29 adults with TBM were randomized (1:1) to receive standard 6-month antitubercular therapy with added oral linezolid dosed at 600 mg twice daily for the first 4 weeks. The primary outcome was all-cause mortality at 1 and 3 months, although the trial was not powered to test this hypothesis. There was no difference in terms of mortality and no major safety concerns were reported. However, the sample size was too small to draw any definitive conclusions and the authors conclude meaningful efficacy needs to be investigated in a larger trial. A similar modestly sized trial in HIV-1 co-infected TBM patients that not only added linezolid but also increased the dose of rifampicin 3.5 times and investigated the use of adjunctive anti-inflammatory aspirin therapy recently reached similar conclusions [7].

In contrast to very significant recent advances brought about by clinical trials activity in PTB [8,9], trials in TBM are infrequent, typically underpowered to demonstrate clinical benefit, fraught by heterogeneity, poorly generalisable outside the populations studied, and thus tend not to influence policy or improve the poor outlook in this condition. Initial hope that increasing the dose of rifampicin with or without additional antibiotics would be effective [10,11] have not clearly been borne out by subsequent investigations [7,12,13]. This is not good progress.

In 2020, COVID-19 induced a plethora of potentially rational choices of existing (and some new) drugs that might reduce mortality. Thousands of clinical trials were launched worldwide; one of the most important and informative was RECOVERY [14]. Within 3 months this platform trial established dexamethasone reduced death by up to one third in hospitalised patients with severe COVID-19 [15]. Evidence followed for the lack of benefit of hydroxychloroquine, lopinavir-ritonavir, colchicine, empagliflozin and azithromycin; and conversely the benefits of monoclonal antibody, tocilizumab and baricitinib therapies (https://www.recoverytrial.net/news). The success of RECOVERY relied on simplified trial procedures, the participation of multiple clinical sites, central randomisation, adaptive design, and frequent data review. To date, 48,506 participants have been recruited from 192 sites.

Could a lessons learnt from such an approach be applied to TBM to accelerate progress? Is there a possibility of a trial that efficiently evaluates multiple interventions for TBM, powered for important clinical endpoints? Obviously the numbers of people developing TBM are much fewer than those developing COVID-19 at its height, and individuals developing TBM commonly live in poor, inaccessible areas with poor access to diagnostics or research-rich resources However we suggest the application of four principles:

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