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EDITORIAL

"Time is brain" also for bacterial meningitis

"Tempo é cérebro" também para meningite bacteriana

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The philosophical principle "time is brain" was initially used in strokes with the intention of showing that the delay in starting therapy would lead to a lower chance of success and that early intervention is the main determinant to limit neuronal damage in the region of ischemic penumbra[1]. This phrase was adapted from the expression "time is muscle," used in cardiology to also point out the importance of early reperfusion therapy in patients with acute myocardial infarction[2], and probably originated from Benjamin Franklin's original aphorism in 1748 "time is money," written in the essay called Advice to a Young Tradesman[3].

In patients with infections of the central nervous system, often caused by potentially treatable agents, "time is brain" as well. Early treatment is of paramount importance and may improve outcomes such as mortality and neurological sequelae.

Bacterial meningitis is a devastating disease with substantial morbidity and mortality, despite treatment with modern antibiotics, advanced intensive care and adjuvant dexamethasone treatment[4]. Reported case fatality rates of bacterial meningitis range from 17 to 40%, depending on causative pathogen and country income status, and long-term neurological and neuropsychological sequelae have been described in up to half of survivors[5].

The outcome depends on whether the doctor suspects acute bacterial meningitis and whether the health system is prepared to make a quick and accurate diagnosis and initiate a rapid and effective treatment. A guideline of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) on bacterial meningitis advised to strive for a door-to-antibiotic time of less than 1h, regardless of whether lumbar puncture has been performed, and the Infectious Diseases Society of America (IDSA) recommends treatment as soon as the diagnosis is "considered likely"[6,7]. Late initiation of antibiotic therapy for bacterial meningitis is associated with increased in-hospital mortality and an unfavorable outcome at discharge[8]. Significant evidence from a variety of observational studies suggests that delayed antibiotic treatment leads to poorer outcomes[9,10,11]. So there seems to be a consensus that the prognosis worsens if initiation of treatment is delayed until a late stage of the disease.

Major progress has occurred over the past twenty years in the prevention of meningitis globally, in particular through the development, marketing and extensive public health use of extremely potent and life-saving vaccines[12]. However, meningitis remains a universal public health challenge due to its worldwide distribution, magnitude, potential transmission, pathogenicity and social relevance. When cases occur, they become immediately high-profile, raising political and media attention universally[12].

The estimated incidence of bacterial meningitis is 0.8 e 2.6 per 100,000 adults per year in developed countries and can be up to 10 times higher in less developed countries[13]. The Global Burden of Disease Study 2016 estimated that the number of global meningitis cases increased from 2.5 million (95% UI 2.19–2.91) in 1990 to 2.82 million (2.46–3.31) in 2016[14]. In 2015, WHO estimated deaths in all ages from meningitis at about 290,000. WHO African Region was estimated to have more than 60% of the deaths for all-cause meningitis[12].

In Brazil, meningitis is a notifiable disease that must be notified within 24 hours. After confirming the cases, they are classified as meningococcal disease, tuberculous meningitis, meningitis by other bacteria, unspecified meningitis, aseptic meningitis, meningitis due to another etiology, Hemophilus meningitis and meningitis by pneumococcus. In the

period from 2001 to 2016, 207,494 cases of meningitis were confirmed for all causes, of which 15.2% (31,605/207,494) were classified as meningitis due to other etiologies, and of these, unspecified bacterial meningitis accounted for 65.1% (20,566/31,605)[15].

One of the operational indicators of meningitis surveillance is the percentage of cases confirmed by laboratory criteria. Meningitis of unspecified etiology shows the need to improve etiological diagnosis. The early diagnosis of meningitis and the identification of the specific infectious agent is desired and helps in the appropriate choice of antibiotic treatment and in the timely institution of control measures such as antibiotic prophylaxis to the contacts of meningococcal disease and meningitis caused by *H. influenza B*, as well as in monitoring the epidemiological profile.

CSF culture is the "gold standard" for diagnosis, and it is obligatory to obtain the *in vitro* susceptibility of the causative microorganism and to rationalize treatment. CSF Gram staining, latex agglutination testing, and polymerase chain reaction (PCR) are additional diagnostic tools that might aid in etiological diagnoses, especially for patients with negative CSF cultures and after initiation of antibiotic treatment. However, the incremental yield of these techniques is sometimes limited[16].

Recently, there has been a shift from CSF culture towards PCR as the main method of pathogen detection. There has been interest in the ability to detect multiple pathogens with one platform, such as multiplex PCR. Point-of-care tests using fast multiplex PCR have been developed, but need clinical validation first, including cost-effectiveness evaluation and implementation studies[5]. PCR is a technique less influenced by the conditions of the sample, and it can be completed on the same day, unlike the bacterial culture, which requires 2-3 days.

In this volume, de Almeida et al.[17] investigated the accuracy of a multiplex PCR assay for acute bacterial meningitis on a substantial number of CSF samples from patients with suspected bacterial meningitis based on CSF cellular and biochemical characteristics, but with negative CSF cultures, as well as cases with proven bacterial meningitis and positive CSF culture results. Multiplex PCR was shown to have a high specificity and negative predictive value, demonstrating the utility of this method in a clinical setting. Multiplex PCR of the CSF proved to be a valuable method for improving the rapidity and accuracy of diagnosis of bacterial meningitis, even in cases with CSF cytochemical characteristics of acute bacterial meningitis but negative culture results.

The "time is brain" aphorism also for bacterial meningitis can help raise awareness of the general population and especially the health services and authorities in the facilitation and importance of early diagnosis and consequent treatment. The planning and implementation of governmental and non-governmental actions are of paramount importance to alert the population to the importance and impact of bacterial meningitis and to improve the speed and accuracy of their diagnosis.

In 2017, two meetings issued calls for a global vision and the defeat of meningitis by 2030. The WHO Secretariat proposes to create a roadmap comprising a clear vision and strategic goals, defined milestones and agreed priorities for research and enhanced control activities. The strategic goals by 2030 are to eliminate meningitis epidemics, reduce cases and deaths from vaccine-preventable meningitis by 80% and provide high quality care for survivors with specific sequelae. Regarding diagnosis and treatment, they should be widely accessible, there should be quality-assured point-of-care tests developed to identify main meningitis pathogens and patients should promptly receive appropriate treatment and supportive care[12].

Bacterial meningitis is an emergency situation and individuals with suspected disease require immediate assessment, diagnosis and treatment. Newer technologies, such as multiplex PCR, and novel diagnostic platforms that incorporate proteomics and genetic sequencing, might help provide a quicker and more accurate diagnosis in the near future.

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