Experience report

Proposal for a simplified approach to suspected meningitis case diagnosis: experience report of a reference service in the state of Piauí, Brazil, 2007-2016

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Abstract

Objective: to describe a simplified protocol to diagnose suspected cases of meningitis. **Methods**: this is an experience report on the approach to diagnosing meningitis at the Tropical Diseases Reference Service in the state of Piauí, Brazil, between 2007 and 2016; information was extracted from the Notifiable Diseases Information System (SINAN) and the laboratory record book; the chi-square test was used to compare epidemiological surveillance indicators based on final meningitis case classification; the Phi coefficient was used to verify the correlation between presumed diagnosis and laboratory-confirmed diagnosis. **Results**: considering the 4,096 cases of meningitis investigated, there was a reduction in the generic classification of meningitis cases from 72% to 47% ($p<0.001$); indicated laboratory investigation profile showed agreement with final meningitis case diagnosis. ($r\phi=0.66$; $p<0.001$). **Conclusion**: a greater proportion of specific etiologic diagnosis of meningitis was achieved while the protocol was in use.

Keywords: Diagnosis;Epidemiology, Descriptive; Cerebrospinal Fluid; Meningitis; Epidemiological Surveillance.

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Introduction

Etiological diagnosis of meningitis using clinical criteria is a challenge for the health care and surveillance services. If, on the one hand, the majority of neurological signs and symptoms of meningitis caused by various microorganisms are indistinct among themselves, on the other hand, the temporal course of the disease can inform inferred etiology of infection.[1,2] Viral and bacterial forms of meningitis (pyogenic) tend to be acute, while infections caused by fungi, mycobacteria, spirochetes, protozoa and helminths are commonly subacute or chronic.[2-9]

Laboratory identification of the causative agent of meningitis is based mainly on the study of cerebrospinal fluid, by means of chemical and cytological analysis, direct examination using Gram staining and India ink, specific antigen or genome detection techniques, imunoenzymatic reactions and cultures using media peculiar to each group of microorganisms.[2,5,9,10] However, in the event of suspected meningitis cases, routine and indistinct use of all available microbiological investigation techniques can lead to high costs for health care services.

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Cerebrospinal fluid is obtained, in limited amounts, through the invasive and uncomfortable diagnostic lumbar puncture (LP) procedure. Repetition of this procedure is not always desirable or feasible, because as the disease progresses, impediments to new punctures can arise owing to the worsening of the patient's neurological status.[2,5,10,11] Therefore, flasks, media and logistics inherent to all diagnostic methods used to test cerebrospinal fluid (CSF) should be available at the time LP is performed.[10-12] Consequently, clear clinical parameters, discernible at the time of initial care, should indicate the main etiologies to be investigated by diagnostic tests.

Initial diagnostic inference in relation to a suspected case of meningitis is important for deciding on empiric treatment.[2,5,9] It is also expected that initial inference guided by the protocol should improve the accuracy of the conclusive diagnosis of meningitis, which will be critical for effective treatment and notification of diseases and injuries on health information systems. Health information systems should reflect the correct causality of diseases, especially so that prevention and control measures can be put in place promptly. In the event of meningitis cases having their nature (bacterial, viral, etc.) inferred only by chemical and cytological criteria (without specific etiological identification), the accuracy of epidemiological data remains low, so that decisions and prophylactic actions in the field of public health are hindered.[13]

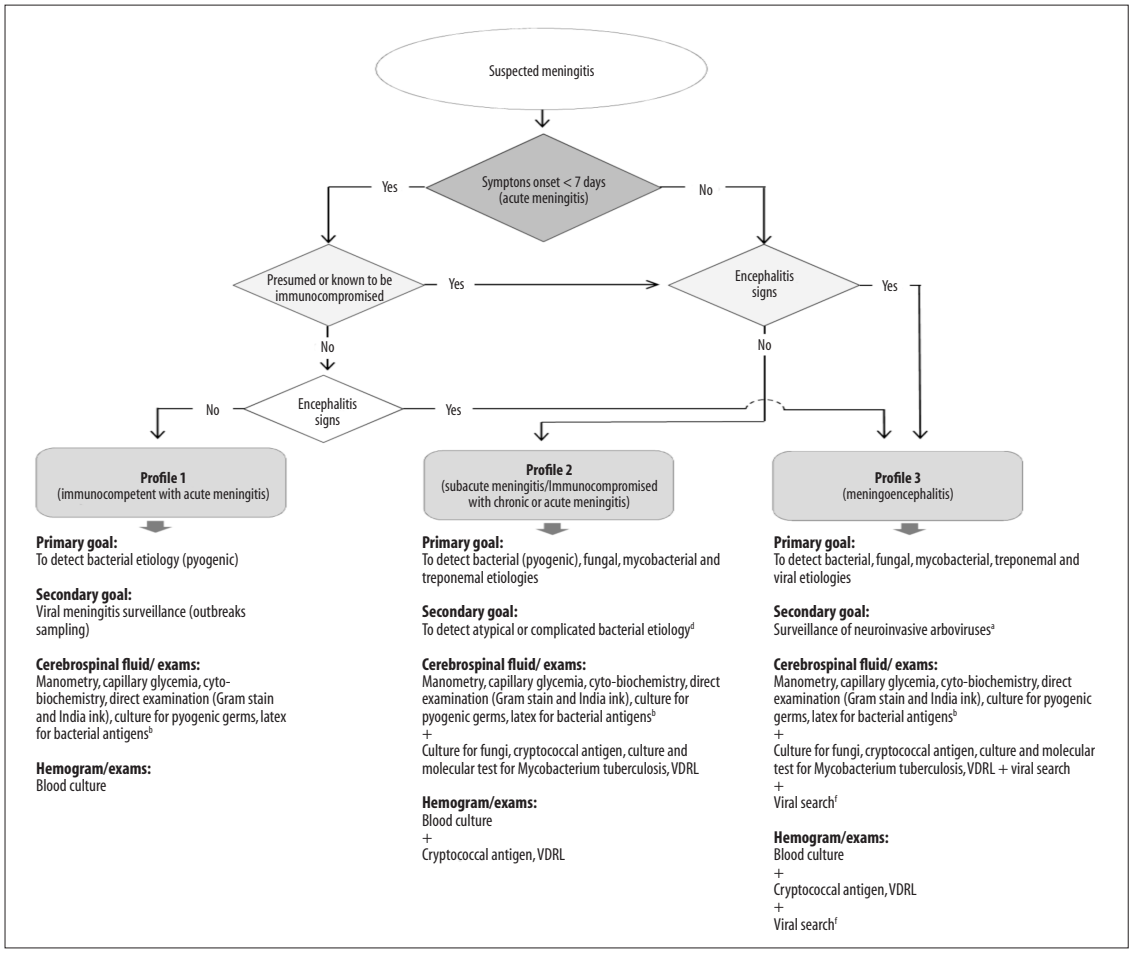
The objective of this study was to describe the use of a simplified protocol for an initial diagnostic approach to suspected cases of meningitis using clinical criteria at a Tropical Diseases Reference Service in the state of Piauí, Brazil.

Methods

This is an experience report to describe a protocol for a simplified initial clinical approach on the final diagnosis of meningitis cases at the Tropical Diseases Reference Service in the state of Piauí.

The protocol in question started being used by the Natan Portella Institute of Tropical Diseases (IDTNP), Teresina, Piauí, in August 2014. The protocol algorithm was applied at the time of the decision to perform LP. Its key premise of checking only three clinical variables informs decision-making regarding the extent of the etiological investigation to be employed. The algorithm was designed so as to meet the therapeutic, prognostic and epidemiological implications of etiological diagnosis of meningeal infections. Before its implementation, there was no consensus among professionals as to the categorization of similar clinical situations (acute, subacute and chronic meningitis, and meningoencephalitis) nor as to the indication of the list of diagnostic tests appropriate for each situation.

The algorithm proposed classifies patients with suspected meningitis into three distinct clinical profiles: profile 1, profile 2 and profile 3 (Figure 1). Each profile provides a standardized and individualized laboratory investigation routine, according to: speed of meningeal symptom onset (acute meningitis verus subacute/chronic meningitis), presumed or known immune status (immunocompetent immunocompromised) and



a) According to the Health Surveillance Guide recommendations.[13]
b) Replace with polymerase chain reaction, if available.
c) Listeria monocytogenes, Brucella sp, Francisella tularensis, Actinomyces sp, Ehrlichia chaffeensis, Nocardia sp, Tropheryma whipplei.
d) Cerebritis, abscess, empyema, septic venous thrombosis, Otomastoiditis.
e) GeneXpert.
f) Viral isolation, polymerase chain reaction, hemagglutination inhibition and immunoenzymatic test.

Figure 1 – Suggested algorithm for simplified initial approach and classification of suspected meningitis cases at the Natan Portella Institute of Tropical Diseases, Teresina, Piauí

signs of brain impairment (presence/absence). These clinical data can be checked easily by the physician in just a few minutes. The sets of laboratory examinations for etiological diagnosis of meningitis cases included in each profile are not mutually exclusive. A progressive and complementary laboratory investigation standard is followed from profile 1 through to profile 3 (Figure 1).

Following the recommended protocol, immunocompetent patients with acute meningitis are categorized in the profile 1 approach to diagnosis (Figure 1). The main goal in this category is to detect the bacterial and pyogenic nature of cases by performing the following tests on CSF: direct examination using Gram staining and India ink, blood agar and chocolate agar culture, detection of bacterial antigens by means of latex agglutination and amplification of bacterial genome by polymerase chain reaction (if available).[5] Blood culture collection is performed for all profiles. The protocol recommends that empiric intravenous antibiotic therapy should be considered for this group of patients until reliable clinical or laboratory evidence supports the exclusion of infection of a bacterial nature;[5,14] it also suggests that samples of some cases of aseptic meningitis presumed to be of a viral nature should be referred to a reference laboratory, as per the recommendations of the Health Ministry's Health

Surveillance Guide.[13] The protocol further recommends direct examination of cerebrospinal fluid using India ink, as this technique can be performed quickly, easily and at low cost. In addition, diagnosis of meningitis caused by fungi may reveal that the individual has immune depletion.[10,12]

Research profile 2 is recommended for immunocompetent patients with subacute or chronic meningitis, and for immunocompromised patients with meningitis regardless of how long they have had it. Additional axams are performed aimed at the diagnosis of fungal, mycobacterial and syphilis infections (Figure 1). When profile 2 is indicated, the threshold for starting antifungal therapy or an anti-tuberculosis drug regimen in addition to or in replacement of antibiotic therapy is reduced.[2,4,6-10] However, the requirement remains to investigate for the presence of bacteria, because bacterial meningeal infections may have subacute course in cases of immunodepression, atypical germs and pyogenic complications (cerebritis, abscess, empyema, septic, venous thrombosis, otomastoiditis), in addition to the prior use of antibiotics on an outpatient basis and orally. Chronic meningitis conditions are different to those of acute meningitis, because they cause symptoms lasting for more than four weeks.[4,6-9] The temporal demarcation between acute and subacute meningitis and between subacute and chronic meningitis is less clear, although it is acknowledged that the symptoms of acute meningitis evolve over a few hours to a few days, those of subacute meningitis over a few days to a few weeks, while those of chronic meningitis evolve between one month and several years.[6-9] Thus, the algorithm proposed established a limit of seven days between acute and subacute meningitis and made no distinction between the temporal evolution of subacute and chronic meningitis, because of the similarity of the etiological agents most frequently involved and the progressive character of the recommended diagnostic investigation.

Patients with suspected meningitis that have overlapping symptoms or signs of encephalitis are categorized in profile 3, regardless of the duration of symptoms and whether their immune status is known or presumed (Figure 1). The protocol recognizes that, like meningitis, meningoencephalitis can also be caused by pyogenic bacteria, fungi, mycobacterial and Treponema; therefore the laboratory tests indicated in profile 1 and 2 are also indicated in profile 3, in addition to testing for viruses (Figure 1). However, viruses gain particular attention when there is underlying impairment of brain parenchyma, owing to the epidemiological importance inherent to this condition and because of the urgency of starting high doses of intravenous antiviral therapy, albeit empirically.[2,4,16-18]

The source population of this study was comprised of meningitis and encephalitis cases investigated at IDTNP between 2007 and 2016.

The study variables were of the categorical/nominal type: (i) meningitis case classification upon completion of epidemiological investigation and (ii) investigation profile indicated at the time of lumbar puncture, according to the flowchart deployed.

Epidemiological classification data were collected as defined at case investigation completion by surveillance teams and input by them on the Notifiable Diseases Information System (SINAN), regardless of the observer's judgment as to additional data contained on the meningitis investigation record held on the database, namely: biochemical cytology examination, hemogram and cultures. The data on the indicated investigation profile were collected from the first lumbar puncture, i.e., at the time of initial suspicion of meningitis, disregarding any subsequent punctures performed on the same patient for the purpose of treatment control or expansion of differential diagnosis.

The data sources were local data held on the SINAN electronic database and the IDTNP laboratory record book of requests for cerebrospinal fluid examinations. Based on a review of the meningitis case investigation records (available on the SINAN database) and the laboratory record book, the annual number of reported cases, the classification of each case (type and criteria), the investigation profile requested and the etiological diagnosis of each case were collected and tabulated on spreadsheets. Diagnosis of meningitis performed by microbiological, immunological and molecular methods reflects the good quality of investigation, as it specifies the causative organism; while classification of cases based only on chemical and cytological examination indicates deficiencies in the laboratory investigation performed.[13]

In order to maximize the statistical significance of the analyses, sampling was performed on a census basis. We studied the laboratory tests and the epidemiological classification of all the meningitis cases investigated by IDTNP over the selected time period.

The final epidemiological classification of meningitis cases and the proportion of cases diagnosed generically

(i.e., only by chemical and cytological criteria), were presented by means of a time series graph. The proportion of cases diagnosed generically and modified over time cases was shown by the chi-square test using BioEstat 5.0. The correlation between presumed etiological diagnosis based on the choice of the investigation profile and the laboratory-confirmed etiological diagnosis was determined by calculating the Phi correlation coefficient Phi ($r\phi$). A 5% significance level and statistical power of 80% were set for the purpose of inferential analyses.

The study project was approved by the Ethics Research Committee of the Federal University of Piauí - Opinion No. 2.059.350/2017; CAAE Registration No.67023317.9.0000.5209. The study project followed the recommendations of National Health Council (CNS) Resolution No. 466 of 12 December 2012.

Results

The time series of 4,096 meningitis and encephalitis cases at IDTNP from 2007 to 2016 shows that, with effect from the year the protocol was implemented (2014), a reduction began in the proportion of cases classified by epidemiological surveillance using only chemical and cytological criteria (Figure 2). Considering the last two years the algorithm was used (2015-2016), there was a reduction in the proportion of cases classified using only chemical and cytological criteria from 72% to 47% ($p<0.001$), when compared to the cumulative proportion observed in the previous eight years (Table 1).

The lowest proportion of cases closed using chemical and cytological criteria was recorded during the period when the flowchart was used (2015-2016), when compared to the proportions of such cases recorded in the four preceding two-year periods (Table 1).

Specific etiology was identified in 48 (28.9%) of the 166 meningitis cases notified and confirmed in 2016. Among the cases in which the causative agent was specified, the indication of profile 1 for investigation based on the presumption of bacterial etiology or the indication of profile 2 based on the presumption of mycobacterial or fungal etiology (Table 2) showed significant correlation with expected diagnostic classification when case investigation was completed ($r\phi=0.66$; $p<0.001$).

Discussion

There was an improvement in the epidemiological classification of meningitis cases by IDTNP during the protocol application period, as proven by the fall in the proportion of cases closed using chemical and cytological criteria and by the increase in the proportion of cases closed using specific laboratory findings, such as direct examination (Gram stain and India ink), and microbiological cultures. There is concordance between the etiological presumption made at the time of initial patient care (reflected in the investigation profile requested) and the final meningitis etiology confirmed by IDTNP.

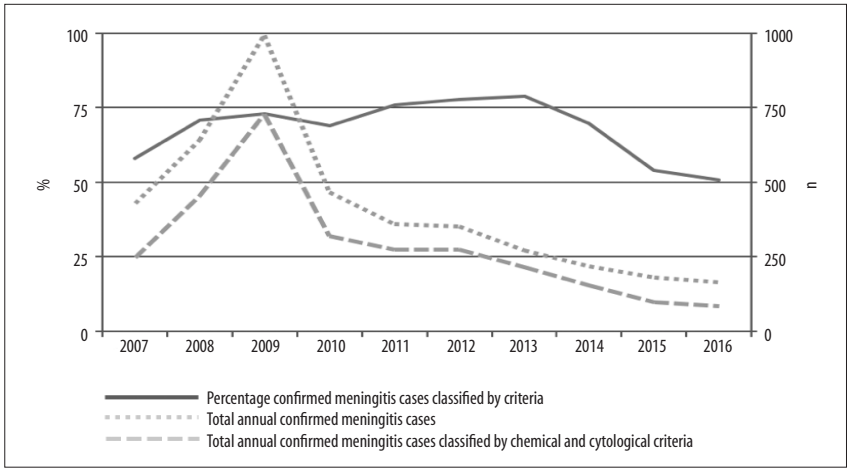


Figure 2 – Meningitis cases classified by criteria, year by year, at the Natan Portella Institute of Tropical Diseases, Teresina, Piauí, 2007-2016

This study was conducted at only one hospital service, the human resources, infrastructure and care provision characteristics of which may not be capable of being extrapolated to other contexts. In addition to comparing asymmetrical intervals of time pre- and post- protocol implementation, the initial period of its use may have been influenced by the learning curve and adaptation to its routine. Counterbalance may have taken place between periods of lower and higher occurrence of meningitis (outbreaks), between the need to confirm the etiology of the outbreak - with consequent greater dedication to specific examinations - and inferring the nature of meningitis using only epidemiological information. In addition, it is possible that the adoption of the protocol motivated the whole team to conduct more detailed anamnesis, collect samples with greater rigor, carry out the examinations with greater dexterity and record data with greater accuracy. These considerations recommend caution in interpreting of the results presented, especially in the absence of studies on similar initiatives in other services. However, if the positive elements mentioned above were present they could also be regarded as a result of adopting of the protocol.

Proposals for approaches to diagnosing meningitis have been made in other countries. In Brazil, however, this publication is pioneer, especially as it combines aspects of clinical diagnosis and laboratory propaedeutics with surveillance actions.[19-22] The algorithm proposed in the protocol acknowledges that the signs and symptoms of meningitis reflect the mechanical or functional impairment of the meninges and, therefore, are not specific to each microorganism involved.[1,3] However, investigating the epidemiological history of the patient informs the suspicion of exposure to specific microorganisms, which makes anamnesis a primordial stage of clinical examination. For instance, acute meningitis caused by free-living amoeba may occur in patients who develop the disease after bathing in an unclean swimming pool. In addition, some clinical examination findings may be important diagnostic indicators, although they have low negative predictive value: hemorrhagic suffusion (Neisseria meningitidis), changes in behavior and personality (herpes simplex, I and II), extrapyramidal disorders (flaviviruses), ataxia (varicella-zoster) and impairment of lower motor neurons (enteroviruses).[1,2,4,9,23-25]

Even though there is some overlap between the causative agents of acute, subacute or chronic infections, the temporal evolution parameter is fundamental for decision-making when following the protocol algorithm, especially with regard to the selection of laboratory diagnosis resources to be employed and the empiric treatment required. For example, cryptococcal

Table 1 – Proportion of confirmed Meningitis cases classified by criteria at the Natan Portella Institute of Tropical Diseases, before and after investigation flowchart implementation, Teresina, Piauí, 2017

Period	Chemical and cytological criteria	Other criteria	Total	P-value
2007-2008	705 (66%)	367 (34%)	1,072 (100%)	<0.001[a]
2009-2010	1,054 (72%)	411 (28%)	1,465 (100%)	<0.001[a]
2011-2012	162 (77%)	553 (23%)	715 (100%)	<0.001[a]
2013-2014	373 (75%)	122 (25%)	495 (100%)	<0.001[a]
2015-2016	165 (47%)	184 (53%)	349 (100%)	–
2007-2014	2,685 (72%)	1,062 (28%)	3,747 (100%)	<0.001[a]

a) Chi-square test comparing the period of flowchart application (2015-2016).

Table 2 – Meningitis cases with specified etiology diagnosis at the Natan Portella Institute of Tropical Diseases, according to indicated laboratory investigation profile, Teresina, Piauí, 2016

Indicator	Bacterial etiology	Fungal or mycobacterial etiology	Total	P-value and Phi correlation coefficient
Profile 1	23	3	26	$p<0.001$[a] e $r\phi=0.66$[b]
Profile 2	5	17	22	
Total	28	20	48	

a) Chi-square test.
b) Phi correlation test.

meningitis has subacute or chronic evolution in immunocompetent patients, although it tends be acute in immunocompromised patients, among whom high fungal load is detected and shortage or even absence of signs of meningeal irritation.[6-8,25]

The algorithm takes into account that chemical and cytological examination of the cerebrospinal fluid should not be used alone in order to presume or discard bacterial infection. Approximately 10% of patients with bacterial meningitis have lymphocytic predominance at initial examination of cerebrospinal fluid.[5,26] Failure to prescribe appropriate intravenous antibiotics could result in great chance of death. Prior use of oral antibiotics and pyogenic parameningeal or intracerebral collections can also modify the chemical and cytological pattern presented. Some virus infections (mumps, lymphocytic choriomeningitis, cytomegalovirus) can result in high cerebrospinal fluid pleocytosis (>1,000 leukocytes/mm³), predominantly neutrophilic and even in hypoglycorrhachia.[2,4,7,14,23,24] Up to two thirds of patients with meningitis caused by enteroviruses whose CSF collection is performed early also have neutrophilic pleocytosis.[4,5,10,12,15] Patients with fulminant meningococcal disease and immunocompromised patients with fungal meningitis may have only slightly increased leukocyte counts or even have acellular CSF.[5,10,15,23-25]

According to the Health Ministry Health Surveillance Guide, if the cause of encephalitic impairment is not clarified in clinical, epidemiological, laboratory or radiological databases, it is recommended that biological samples be sent to a reference laboratory to investigate for neuroinvasive arboviruses.[13]

The experience of the Natan Portella Institute of Tropical Diseases in the period the protocol was used revealed: (i) presumed etiology of meningitis cases based on simplified clinical parameters and (ii) improvement of epidemiological surveillance indicators. Inferring the most likely causative agents for each case at initial patient care can contribute to the adequate selection of which cerebrospinal fluid analyses to perform and inform the initial treatment decision. As this is an experience of just one service, the protocol should be tested in research in other contexts, and thus inform relevant changes to meningitis surveillance guidelines.

Authors' contributions

Vieira MACS, Costa CHN, Costa DL and Eulálio KD drew up the algorithm studied here. Lima Neto AS, Lima JCV, Sousa JVB and Santos MO contributed to the laboratory data collection. Campelo LLD and Almeida Neto WS collected data from the SINAN system. Amaral EJLS, Batista FMA, Nascimento GV and Rodrigues MDR provided institutional support to the implementation of the work. All the authors participated in the design of the study, data analysis and interpretation, drafting, review and have approved the final version of the manuscript and declared themselves to be responsible for all aspects of the study, ensuring its accuracy and integrity.

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