Microbes, Infection and Chemotherapy

REVIEW ARTICLE

https://doi.org/10.54034/mic.e1357

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Lactate as an important biomarker of cerebrospinal fluid in infectious diseases of the central nervous system: A comprehensive literature review

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Abstract

Central nervous system (CNS) infections are a group of diseases, where meningitis (associated or not to neurosurgical interventions) and bacterial ventriculitis have been studied for many years in order to establish early diagnosis methods through direct therapy to reduce morbidity and mortality in this population. Analysis of the cerebrospinal fluid (CSF) is an important source of information for diagnosis of neuroinfection. Lactate concentration in the cerebrospinal fluid has a value independent of plasma because it does not cross the blood-brain barrier, therefore, constitutes the end-product of the bacterial anaerobic glycolysis being the primary source of lactate in the CSF. Therefore, it has a great tool in the diagnostic approach of bacterial meningitis, however, reference values are not warranted. Objective: The authors present the latest scientific evidence on the use of lactate as a diagnostic method for two neurological pathologies with highest incidence on population, establishing a translational approach to clinical practice. Methods: A comprehensive literature review was carried out. We describe the results of a structured search based on keywords infection, meningitis, ventriculitis, bacterial, cerebrospinal fluid, and lactate, vía Medline, Scopus, WoS, EMBASE, and LATINDEX databases. Conclusion: Lactate in a CSF sample is useful to determine the bacterial etiology in patients with suspected meningitis. CSF lactate value equal or higher than 4 mmol/l could indicate bacterial meningitis about 90% of probability. Lactate value is identical in patients with ventriculitis; however, it cannot be established as neuroinfection, therefore, we should use another diagnostic method.

Key word: infection, meningitis, bacterial, ventriculitis, cerebroespinal fluid, lactate.

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Submitted: february 12, 2021
Reviewed : february 22, 2021
Approved : march 23, 2022

How to cite: Vélez-Páez JL, Rueda-Barragán FE, Torres-Carpio DA, Guerrero FM, Romero JJ, Vásconez-González E, Ortíz-Prado E. Lactate as an important biomarker of cerebrospinal fluid in infectious diseases of the central nervous system: A comprehensive literature review. Microbes Infect Chemother. 2022; 2: e1357

Introduction

According to the CDC (1), in 2019, the incidence of meningococcal meningitis in the United States, Australia and South America was 0.12 to 3 cases per 100000 population. At the European level (2) a similar incidence of 1 to 2 cases per 100000 population annually is mentioned.

The Gold Standard (2) to establish a diagnosis is the examination of cerebrospinal fluid (CSF) in which, depending on its characteristics, we can discriminate whether it is a viral or bacterial infection, however, in many cases this is difficult to differentiate, hence new biomarkers are being used to help us discern the diagnosis of a SN infection of bacterial etiology allowing the birth of lactate as a biomarker in CSF.

The first observations were made by Levinson (3) in 1917, where he detected those patients with meningococcal meningitis had a pH lower than expected, having as a possible cause the accumulation of lactate in the CSF, which was corroborated by Kilian (4) in 1926, who demonstrated that patients with pneumococcal and meningococcal meningitis reached higher lactic acid values than healthy patients.

Lactate exists in two isomeric forms (3):

- L - lactate: the isomer measured in commonly used assays, and the only form produced by human metabolism.
- D - lactate: is produced by bacterial metabolism, and can accumulate in patients with gastric bypass surgery and short bowel syndrome. It is one of the causes of metabolic acidosis with elevated anion gap.

CSF lactate concentration is independent of blood lactate, reflecting the fact that, at physiological pH, lactate is fully ionized and therefore crosses the blood-brain barrier at a slow rate; as such, it is a useful marker of brain metabolism (5).

The most important source of lactate in the SN is brain tissue, including neurons and glia cells. In infectious states such as bacterial meningitis, generalized cerebral edema is produced, which decreases cerebral blood flow (CBF) and generates inflammation of blood vessels that alters cerebral autoregulation, with vasospasm and thrombosis leading to ischemia, glycolysis and anaerobic metabolism. Additionally, the presence of pro-inflammatory cytokines that invade the brain, reduce oxygen absorption and cause tissue hypoxia, invasion of neutrophils into the subarachnoid space that aggravates the already established anaerobiosis; to which is added the bacterial production of lactate, which alone contributes 10% of its elevation (6).

Based on this pathophysiological knowledge, lactate is currently considered an excellent biomarker of bacterial infection of the SN, and many guidelines include its evaluation in the CSF study, considering that it is a relatively affordable and easy to interpret test. The measurement of lactate in cerebrospinal fluid requires basic laboratory equipment, and its processing time is relatively fast (approximately 2 hours). It is a low-cost test and has high reproducibility. It is available in resource-limited settings.

Samples for lactate analysis should have low red blood cell concentration, because red blood cells possess a high lactate content, therefore, its minimum recommended volume is 0.5 ml. Processing is recommended within 60 minutes of obtaining the sample. If the analysis is delayed for more than 24 hours, the sample should be refrigerated to avoid falsely high values (30).

In the following paragraphs we will write the results of a structured search with the keywords infection, meningitis, ventriculitis, bacterial, cerebrospinal fluid and lactate, both in English and Spanish in the Medline, Scopus, WoS, EMBASE and LATINDEX databases.

Usefulness of lactate as a diagnostic marker of meningitis

Meningitis has varied etiological causes such as bacterial, viral, fungal or parasitic. The first two causes are the most prevalent. The etiology depends on factors such as age, immunosuppression states, geographical location, etc.

Under this scenario, is difficult to identify the causal germ, therefore, guidelines recommend starting an empirical treatment considering local epidemiology and other risk factors. In addition, culture collection should be carried out to target treatment based on results, however, inadequate procedures can be deleterious to the patient's prognosis.

In general terms, meningitis has a mortality rate of 21% (8). In the United States, there is evidence of 2.5 cases per 100,000 inhabitants per year (9).

It is for this reason those new methods have been sought to allow an early diagnosis of the microbiological etiology, demonstrating that elevated lactate in CSF has a high correlation with bacterial infection; his study began in 1917 where Levinson already demonstrates the elevation of lactate in CSF, multiple studies have validated this theory.

Thus, the latest IDSA guidelines published in 2004 (10) refer to the usefulness of CSF lactate to distinguish bacterial from viral etiology. In these guidelines it is mentioned that in the study of CSF it is not possible to affirm that a single marker is definitive of bacterial meningitis, that is why they combine a series of parameters: glucose concentration < 34 mg/dl, serum glucose/CSF ratio < 0.23, proteinorrachia, leukocytosis with predominance of neutrophils, reaching this global assessment 99% certainty of bacterial etiology; however this strategy should not be used for decision making regarding therapy that is why the exploration of other markers is done and they mention that the elevation of 4. 2 mmol of lactate in CSF correlates with bacterial etiology with high sensitivity and specificity value (table 1), but despite its excellent clinical correlation, the guidelines indicate that other processes may be responsible for this elevation, among them are reported:

- Ischemia/hypoxia.
- Vascular involvement.
- Seizures, especially status epilepticus and focal seizures with loss of consciousness.
- Cerebrovascular event.
- Malignancy.
- Mitochondrial disorders.
- Inherited metabolic disorders.
- Subarachnoid hemorrhage.
- Cranioencephalic trauma.
- Anoxic brain injury.
- Hypoglycemic coma.

Therefore, they mention that its measurement is not very specific and that in patients with suspected community bacterial meningitis it is not recommended, having a level of recommendation (D-III) which does not make it very clear whether it should be used or not within the guidelines of these guidelines; but they do mention the usefulness of lactate in the diagnosis of meningitis secondary to neurosurgical interventions.

On the other hand, several prospective and retrospective studies, and a well-designed meta-analysis (described in Table 1), have found that lactate levels greater than or equal to 3.5 mmol/L have a high sensitivity and

Table 1

Summary of the different studies to determine the usefulness of lactate in bacterial meningitis. AUC: area under the curve VVP: positive predictive value, NPV: negative predictive value, cerebrospinal fluid CSF

Study name and year of publication	Authors	Type of study	Universe	Outcome	Sensitivity (%)	Specificity (%)	AUC	PPV (%)	NPV (%)
Practice Guidelines for the Management of Bacterial Meningitis (2004)	Tunkel et al (9)	Clinical Practice Guide (D-III)		Validate that lactate values> 4 mmol / l in CSF correlate with bacterial infection	96	100		100	97
Practice Guidelines for the Management of Bacterial Meningitis (2004)	Tunkel et al (9)	Clinical Practice Guide (B-II)		Demonstrate that lactate values> 4 mmol / l in neurosurgical patients are higher than the serum glucose / CSF ratio	88	98		96	94
The UK joint specialist societies guideline on the diagnosis and management of acute meningitis and meningococcal sepsis in immunocompetent adults (2016)	MCGiLL et al (11)	Clinical practice guide (2b)		Differentiate the bacterial etiology from the rest of the possibilities with values> 3.89 mmol / l (35 mg / dl) in CSF lactate	93, disminuye a 50 si se mide después de administrar antibióticos	96			
Diagnostic accuracy of cerebrospinal fluid lactate for differentiating bacterial meningitis from aseptic meningitis (2011)	Sakushima and cols (13)	Meta-analysis	1885	Lactate values greater than 3.89 mmol / l discriminate between bacterial and aseptic meningitis	93	96	1		
CSF lactate level: a useful diagnostic tool to differentiate acute bacterial and viral meningitis (2009)	Ali Hassan Abro and cols (14)	Observational study	95 patients with 53 bacterial and 42 viral meningitis)	Values greater than 3.8 mmol / l are consistent with bacterial etiology (p <0.0001)					
Performance of lactate in discriminating bacterial meningitis from enteroviral meningitis (2019)	Domingues Renan Barros and colaboradores (12)	Retrospective study	1,187 CSF samples (662 bacterial etiology, 525 enterovirus)	Values greater than 3.33 mmol / l in CSF are highly suggestive of bacterial meningitis	84	99	1		
Predictive Value of Cerebrospinal Fluid (CSF) Lactate Level Versus CSF/Blood Glucose Ratio for the Diagnosis of Bacterial Meningitis Following Neurosurgery (1999)	Leib S.L et al(7)	Retrospective study	73 patients: established bacterial meningitis (12) possible bacterial meningitis (14) non-bacterial meningeal syndrome (47)	Lactate values greater than 4 mmol / l are higher than a CSF / blood glucose ratio <0.4 to determine bacterial etiology	88 vs 77	98 vs 87		96 vs 77	94 vs 87
Utility of lactate in cerebrospinal fluid as a biomarker of bacterial meningitis (2018)	Celis-Galeano Aleida and cols (15)	Retrospective study	103 patients	To determine the usefulness of lactate in cerebrospinal fluid as a biomarker of bacterial meningitis, with a value of 4 mmol / l	91	92			
Cerebrospinal fluid lactate concentration to distinguish bacterial from aseptic meningitis: a systemic review and meta-analysis (2010)	Huy N. et al (10)	Systematic review and meta-analysis	25 studies, 909 patients with aseptic meningitis, 783 patients with bacterial meningitis	To assess the precision of lactate (cut-off point greater than or equal to 3.5 mmol / L) in the differential diagnosis between bacterial meningitis and aseptic meningitis.	96	94	0,98		

specificity to distinguish acute bacterial meningitis from acute viral meningitis (31).

The diagnosis of post-surgical meningitis is more elusive than that of a community-acquired infection. None of the classic findings, both clinical and biochemical, are specific nor have they reached an adequate positive or negative predictive value in patients undergoing neurosurgical procedures. Classic signs such as headache, meningeal signs and cranial nerve abnormalities are difficult or impossible to confirm such a diagnosis because many of these patients are sedated, ventilated or have pre-existing neurological deficits. However, there is relevant evidence supporting the use of CSF lactate with a cut-off value >4 mmol/L indicative of bacterial infection, being even higher than the serum glucose/CSF ratio, reaching a sensitivity of 88% and specificity of 98%. However, there may be cases with false positive results even with an apparently normal lactate level, which does not completely rule out an established infectious process.

Currently, CSF lactate is included as a diagnostic biomarker in the management algorithms for patients undergoing neurosurgical procedures who develop bacterial meningitis during their evolution.

In contrast to the IDSA guidelines and being more current (2016), the United Kingdom consensus on the diagnosis and management of meningitis and meningococcal septic shock in immunocompetent patients (11) mentions that in ALL patients undergoing lumbar puncture (LP) lactate should be measured before starting antimicrobial therapy without its measurement delaying the initiation of therapy with a level of evidence and recommendation 2B. It is mentioned that its measurement, added to glucose and protein values, is very useful to differentiate bacterial etiology from the rest of the possibility, said guide mentions that a lactate value higher than 3. 89 mmol/l (35 mg/dl) is useful to distinguish bacterial from viral etiology as long as it is measured before administering antimicrobial therapy, since if it has been measured after initiating this therapy, its sensitivity decreases to 50%, its high negative predictive value (NPV) makes it a useful tool not only for diagnosis but also to evaluate the response to treatment.

The following is a summary of the evidence found in the literature supporting lactate measurement as a diagnosis of bacterial meningitis (Table 1).

In addition to this extensive review, we include the study presented by Bruneira Peres et al (14) where they demonstrate the usefulness of CSF markers in the diagnosis of bacterial meningitis (Figure 1).

After this extensive literature review, we can conclude that measuring lactate in a CSF sample is very useful to determine the bacterial etiology in patients with suspected meningitis, if possible, it should be measured before administering antibiotics without this measurement delaying the onset of antibiotics, if we reach these conditions and seeing a CSF lactate value greater than or equal to 4 mmol / l our patient will have bacterial meningitis with a greater than 90% certainty; Its usefulness lies in the fact that it will allow us to better direct the antimicrobial therapy and perhaps it can be used as a follow-up tool to assess the patient's response, although studies are still needed to validate this hypothesis.

Usefulness of lactate measurement in ventriculitis

Ventriculitis is defined as the inflammation of the ependymal lining of the cerebral ventricles, generally secondary to infection (17), although it can be indolent at first, however, it reaches high mortality rates, even more so when it occurs after the treatment of meningitis. Currently, we do not have clear criteria to support the definition of ventriculitis due to the unspecificity of its symptoms and its multifactorial etiology, so it's possible etiologies may be the following:

- Meningitis
- Brain abscess
- Iatrogenic
- Associated with the presence of catheters, ventricular drains, etc.
- CSF shunting
- Intrathecal therapy
- Neurosurgery

As we can see, a large part of the etiology is related to external manipulation. Thus, the IDSA (18) mentions that when ventriculitis is suspected, it should be managed as if it were associated with health care, which should lead us to think that we will be treating more "complex" and perhaps resistant germs.

On the one hand, we have ventriculitis associated to meningitis (17) or also called pyogenic ventriculitis which is more frequent in children and should be suspected whenever the patient shows signs of recurrent meningitis despite the treatment received, another type is ventriculitis associated to catheters which reaches an incidence of up to 45%, ventriculitis associated to external ventricular drainage (EVD) in 22%, Martin et al (19) publishes the percentage of infection associated to neurosurgical procedures and implantation of devices (table 2).

Bearing in mind that many of these entities originate after a medical procedure, it is to be expected that many germs with a high rate of resistance to first line treatments are involved. Infections by gram-negative germs have been reported (20), which correlates with the report of Martin et al (19) where it is mentioned that in recent years there has been a tendency for non-glucose fermenting gram-negative bacteria (Pseudomona spp., Acinetobacter spp, Burkholderia) are the main causes of nosocomial infections, but it also mentions that a high percentage of infections are still caused by gram-positive germs, with Staphylococcus epidermidis and Staphylococcus aureus being the main Gram-positive bacteria found in samples from patients undergoing VED placement.

Regarding the diagnosis, the IDSA 2017 guidelines

(18) mention that this should be made based on the clinical history, which can be diverse.

Table 2

Infection rates of most common neurosurgical procedures PCI: intracranial pressure Taken from reference 19

Surgery	Risk of infection (%)
Craniectomy	1-24.4
Craniotomy	0,32-12
Spine surgery with instrumentation	3-Jul
Spine surgery without instrumentation	2
Lumbar puncture	1 for every 50,000 patients
Temporary devices	
Ventriculostomy (DVE)	Feb-22
PCI monitor in parenchyma	< 0.2
Lumbar drainage	5
Permanent devices	
Ventricular shunt	8 (children) 4-17 (adults)
Spinal cord medication pumps	6
Deep brain stimulators	1

Currently, the diagnosis of ventriculitis related to intraluminal devices (VED, lumbar drainage) does not have a Gold Standard that allows discriminating an infection from another etiology. Infection associated with drainage devices is relatively common, occurring in 5-15% of inserted devices, especially in the first four weeks after placement (18). The usual signs and symptoms are nonspecific and often overlap with other neurological conditions in patients with CSF drains. Decreased Glasgow Coma Scale and the presence of fever have been present in less than one-third of these patients in retrospective and cohort studies. The presence of CSF cultures and Gram test associated with pleocytosis establishes the diagnosis of this entity, however, they are highly specific but poorly sensitive.

The use of biomarkers, such as serum procalcitonin (PCT) level and CSF lactate are diagnostic parameters that have been studied lately, however, they have shown mixed results regarding their usefulness.

We can establish that the meeting of clinical, biochemical and microbiological criteria makes the diagnosis more accurate in the suspicion of infection associated with the use of a catheter in neurosurgical pathology, giving greater importance to Gram staining and isolation of germs in CSF cultures.

The following is a summary of the current evidence in the world literature on the usefulness of lactate in the diagnosis of bacterial ventriculitis (Table 3).

Although it is true that values higher than 4 mmol/l of lactate measured in CSF are highly suggestive of bacterial infection in ventriculitis, nevertheless, there is still no certain evidence that indicates the previous premise, since when reviewing more closely the evidence presented there are studies that mention that having values at 3.6 mmol/l does not rule out the possibility of infection (18), likewise in 20% of patients with CSF derivation (22) lactate values higher than 4 mmol/l were recorded without meaning active infection.

A fundamental point to understand is the puncture site for the CSF sample, establishing between lumbar puncture and ventricular puncture. Thus, Almeida et al (24) in 2019 showed that while it is true that lactate values higher than 4 mmol/liter are highly suggestive of bacterial infection. These values may vary depending on the puncture site, showing that lactate taken by lumbar puncture was twice as high as that collected by ventricular puncture.

In view of this review, we can mention that, although lactate values above 4 mmol/l are suggestive of bacterial infection, in patients with health care-associated ventriculitis, the diagnosis of neuroinfection cannot be fully established. By physiopathology, the elevation can occur after a previous manipulation, therefore, we should use some other diagnostic method that allows us to corroborate the diagnosis of ventriculitis. A high lactate level in a patient with a low probability of infection probably requires reconsideration of other etiologies. On the other hand, low lactate levels in a patient with a high probability of device-associated neuroinfection do not exclude the diagnosis of bacterial infection, especially if the patient has had previous antibiotic treatment.

Translational approach

Bacterial meningitis is the main cause of CNS infection, which can progress rapidly leading to irreversible brain damage. As a consequence, there is a decrease in cerebral blood flow, cellular hypoxia, anaerobic catabolism with lactate formation and a considerable increase in CSF.

Lactate in CSF is the final product of anaerobic glycolysis of both leukocytes and bacteria, being therefore, bacterial metabolism in case of neuroinfection, the main source of lactate in this body fluid (25).

In practice, it is important to highlight the usefulness of a biomarker such as lactate, which constitutes a fast and accessible element for the timely identification of bacterial infections at the CNS level, allowing immediate treatment decisions with antimicrobial agents. In addition, it has been described as useful during the course of the disease, since its normality indicates a good prognosis (26).

As we have previously reviewed, lactate is an excellent biomarker of hypoperfusion and tissue hypoxia in patients with sepsis; however, in CNS infection of bacterial etiology, scientific evidence to date has allowed us to recommend its use with greater relevance in patients undergoing neurosurgical interventions.

Table 3

Summary of the different studies to determine the usefulness of lactate in bacterial ventriculitis. AUC: area under the curve VVP: positive predictive value, NPV: negative predictive value, cerebrospinal fluid CSF

Study name and year of publication	Authors	Type of study	Universe	Outcome	Sensitivity (%)	Specificity (%)	AUC	PPV (%)	NPV (%)
Infectious Diseases Society of America's Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis, Clinical Infectious (2017)	Tunkel et al (24)	Weak recommenda tion clinical practice guideline with a moderate level of evidence		Usefulness of lactate as a marker of bacterial infection	90	90			
Use of ventricular cerebrospinal fluid lactate measurement to diagnose cerebrospinal fluid infection in patients with intraventricular haemorrhage (2008)	Wong et al (25)	Prospective study	16	Usefulness of lactate to determine infection in a patient with intraparenchymal hemorrhage who underwent PVD placement				60	100
Characteristics and Treatment Outcome of Cerebrospinal Fluid Shunt–Associated Infections in Adults (2008)	Conen and cols (22)	Retrospectiv e study	78 patients	To determine the usefulness of lactate with values> 4 mmo / l in patients with CSF shunt is a marker of infection; 20% had values greater than 4 mmol / l without this translating infection					
CSF lactate is not a reliable indicator of bacterial ventriculitis in patients with ventriculostomies (2017)	Hill et al (26)	Retrospectiv e study	467 CSF samples	Usefulness of lactate in patients with ventriculostomy as a marker of infection	70	70	0,82		

The value of lactate as a diagnostic biomarker of bacterial meningitis, establishes a cut-off point higher than 4 mmol/l in most of the reported works, reaching a sensitivity and specificity higher than 90% (27), however, its interpretation must be performed in parallel with clinical findings.

Normal or discrete lactate levels have been reported in cases of fungal or viral meningitis.

The association of other biomarkers such as glucose, proteins, leukocytes, serum glucose/CSF ratio, constitute diagnostic support to determine a bacterial infection, however, there are other pre-existing conditions that could increase or decrease their absolute values, being non-specific now of making decisions.

There are other metabolic entities that could affect the CNS, such is the case of pyruvate dehydrogenase deficiency and disorders of the respiratory chain, which would also elevate lactate concentrations, being this biomarker together with pyruvate tools of great importance for the differential diagnosis of atypical pathologies (28).

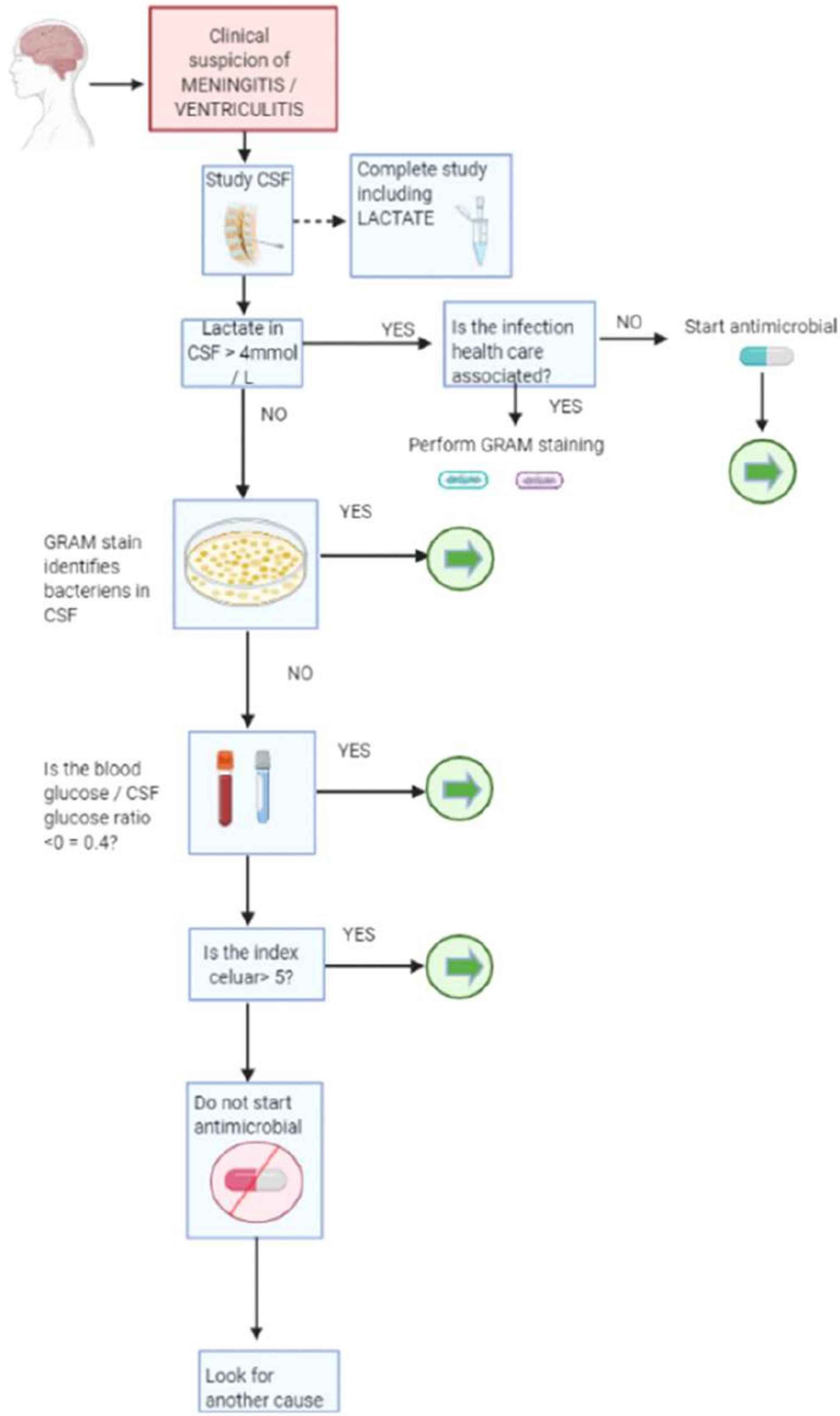
Analyzing another of the entities studied as ventriculitis, there are international consensus that partially support the use of lactate as a diagnostic biomarker, having several limitations when establishing a cut-off point. Their recommendations are aimed at using other parameters to establish a clear diagnosis, especially in patients with VED, in which the initiation of antimicrobials becomes a challenge.

Currently, lactate measurement methods are heterogeneous, being amperometric, which use a sensitive electrode with a silver cathode and a platinum anode. Amperometric measurement is a low-cost method, available even in small laboratories, and has been shown to be equivalent in performance to other more complex assays validated in CSF (enzymatic measurement, ultraviolet light) (32). In addition, there are spectrophotometric methods that measure the absorbance of NADH, chemical oxidation methods using permanganate or manganese dioxide to degrade lactate to acetaldehyde, the latter measurable through spectrophotometry or chromatography, however, its use is rare (29). The performance in the form of its measurement to establish a diagnostic value is a matter of controversy at present.

Finally, after performing a structured review on CSF lactate, we have created a diagnostic flowchart for patients with suspected bacterial meningitis or ventriculitis. Our goal is to simplify the use of this biomarker associated with other diagnostic support entities ensuring appropriate treatment quickly and safely, avoiding the unequivocal use of antibiotics. (Figure 1).

Figure 1

The diagnostic flowchart in meningitis and bacterial ventriculitis using lactate as a biomarker in CSF for the initiation of antimicrobial therapy



Conclusion

Measuring lactate in a CSF sample is useful to determine the bacterial etiology in patients with suspected meningitis, if possible, it should be measured before administering antibiotics without this measurement delaying the onset of the same, a lactate value in CSF greater than or equal to 4 mmol / l means that a patient will have bacterial meningitis with security greater than 90%, however, the same lactate value in a patient with ventriculitis cannot be established with total security that it is a neuroinfection due to that, pathophysiologically, the elevation can occur after a previous manipulation, therefore, we should use some other diagnostic method.

List of abbreviations

CNS: central nervous system
CSF: cerebroespinal fluid
CDC: centers for disease control and prevention
IDSA: infectious diseases society of America
LP: lumbar puction
NPV: negative predictive value
EVD: external ventricular drainage
PVD: peritoneal ventricular drainage
PCT: procalcitonin
NADH: nicotinamide adenine dinucleotide

Authors' contributions

JLVP, DT, FR contributed with the citation extraction from the international databases and contributed equally to the preparation of the first draft of the manuscript. JLVP FMG JJR contributed with the translational approach and with the elaboration of the algorithm that we have established, EVG and EOP were in charge of the critical appraisal of the literature, the elaboration of the figure and the elaboration of the final version of the manuscript.

Competing interests

The authors declare that there is no conflict of interest.

Funding

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