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Abdullaev Azizbek Subhonalievich

Sobirov Muhammadjon Soyibjon ugli

Assistants

Department of Anesthesiology - Reanimatology,

pediatric anesthesiology – resuscitation

Andijan State Medical Institute

ETIOLOGICAL, DIAGNOSTIC AND MORPHOLOGICAL FEATURES OF SEVERE PNEUMONIA (LITERATURE REVIEW)

Abstract: The problem of treating patients with pneumonia has been in the center of attention of specialists in various fields for a long time, but still does not lose its relevance. According to the US National Nosocomial Infection Surveillance System (NNIS), hospital-acquired pneumonia is the third most common form of hospital-acquired infections (after surgical wound infections and urinary tract infections). The incidence of nosocomial pneumonia reaches 250,000 cases per year, which is from 13 to 18% in the total structure of nosocomial infections, and this complication steadily ranks first in terms of mortality.

Key words: severe pneumonia, artificial lung ventilation, ventilator associated pneumonia, multi-resistant microorganisms.

Pneumonia is understood as an infectious disease characterized by focal lesions of the respiratory parts of the lungs with intraalveolar exudation and accompanied by a febrile reaction and intoxication. There are the following types of pneumonia; a) out-of-hospital (out-of-hospital); b) nosocomial (hospital; nosocomial); c) aspiration and abscess; d) pneumonia in immunodeficiency states (congenital immunodeficiency, HIV infection; neutropenia), etc. Hospital pneumonia is understood as pneumonia that developed 48 hours or more after hospitalization of the patient in a hospital (provided that there is no infection, in the incubation period at the time admission of the patient to the hospital). Hospital ventilator-associated pneumonia (VAP) is a special case of hospital-acquired pneumonia (HP) that develops in patients with mechanical ventilation (ALV).

The problem of treating patients with pneumonia has been in the center of attention of specialists in various fields for a long time, but still does not lose its relevance. For example, in the USA it is registered annually; 4-5 million cases of community-acquired pneumonia; moreover, 25% of patients require hospitalization [1].

Despite the large arsenal of drugs, this disease ranks seventh among the causes of death [2].

According to MIS. Niederman et al. [1] the death rate among patients with pneumonia is 22 cases per 100,000 population per year.

According to the US National Nosocomial Infection Surveillance System (NNIS), hospital-acquired pneumonia is the third most common form of hospital-acquired infections (after surgical wound infections and urinary tract infections). The incidence of nosocomial pneumonia reaches 250,000 cases per year, which is from 13 to 18% in the general structure of nosocomial infections, and this complication steadily ranks first in terms of mortality [3, 4, 5, 6].

Isolation of pneumonia developing against the background of artificial ventilation (ventilator-associated or VAP) into a separate nosological form is associated with its special etiology and pathogenesis, as well as with the severity of the condition of patients who are at risk of infection during mechanical ventilation.

The occurrence of VAP almost always leads to lengthening of hospital stay, cost of treatment and an increase in the risk of an unfavorable outcome [7, 8, 3, 4].

In patients with VAP, mortality ranges from 24 to 65% and increases to 76% if the infection is caused by multi-resistant microorganisms [8]. One of the main causes of death is acute respiratory failure, which often develops as a component of multiple organ dysfunction in the presence of severe sepsis.

The use of invasive ventilation facilitates the collection of material from the lower respiratory tract for microbiological examination. In this regard, most of the data on the causative agents of HP were obtained from patients who underwent mechanical ventilation and, accordingly, were diagnosed with VAP. These data are usually extrapolated to all patients with hospital-acquired pneumonia. There are no data in the modern literature regarding the differences in the etiology of severe VAP and pneumonia, which required mechanical ventilation. At the same time, the study of the microbiological landscape of the intensive care unit (ICU) makes it possible to determine the optimal empirical therapy and monitor the effectiveness of measures to prevent infection [9].

Due to the presence of certain patterns in the etiology and pathogenesis, hospital pneumonia is divided into early and late (before or after 5 days from admission to the hospital). Early pneumonia is most likely associated with aspiration during the development of ARF or with intubation, late - due to changes in conditions from the gastrointestinal tract. Even if all precautions are taken at the time of intubation, there is a mechanical transfer of microflora from the upper respiratory tract to the tracheobronchial tree [10].

A competing mechanism as the root cause of the early form of VAP is aspiration of gastric contents in the period immediately preceding or during intubation. As a result, in patients with early TP and VAP, the most frequent etiological agents are pathogens that colonize the URT and the upper gastrointestinal tract: methicillin sensitive Staph, aureus, Strep, pneumoniae, Enterobacteriacae, H. Influenze.

Apparently, in late pneumonia, the most common way of penetration of infection into the lower respiratory tract is microaspiration of the contents of the oropharynx infected with pathogenic bacteria. In this case, an important role is played by the phenomenon of bacterial translocation from the stomach and small intestine into the oropharynx, and then the entry of contaminated secretions into the lower respiratory tract [10,3,11].

In addition, pathogenic microorganisms can enter the respiratory tract exogenously - as a result of cross-infection from other ICU patients (through unwashed hands and infected gloves of medical staff or when using poorly processed reusable medical instruments, apparatus, equipment, etc.) [12, 13, 14, 10].

In the etiology of late HAP (in contrast to early HAP), the leading role is played by hospital pathogens characterized by multiple resistance to antibacterial drugs (hospital micloflora): Pseud. aeruginosae, AcinetoBacter, methicillin-resistant Staph. Aureus, etc.

Judging by the publications, there has not been any significant dynamics in the microbiological spectrum in recent years; the proportion of multi-resistant microorganisms in the etiology of VAL remains extremely high. The results of treatment of severe pneumonia also do not significantly improve, which forces not only to look for new approaches to antibiotic therapy, but also to improve other methods of treatment, for example, to change approaches to respiratory therapy (more extensive use of NVL) [15, 16].

In order to optimize preventive strategies, several studies have been carried out in relation to risk factors for the development of HAP. The risk factors for the colonization of pathogenic microorganisms and the development of pneumonia are largely similar, which partly confirms the modern understanding of the pathogenesis of HAP. Independent risk factors for the development of VAP, the statistical significance of which has been confirmed in special studies, are presented in Table 1 [8].

When analyzing the table, it can be seen that the occurrence of HP can be caused by both objective (systemic) and subjective (non-systemic) reasons that depend on the organization of the treatment process in a particular institution. It is forbidden; to argue that the significance of the latter factor and the influence of its formation on the microbial spectrum of the institution is ignored, but the attention to it in the literature is not as close as to other issues.

Diagnostics. Currently, none of the diagnostic methods has sufficient sensitivity and specificity to reliably diagnose VAL; those. cannot claim to be the "gold standard" of diagnostics. Until now, the diagnostic criteria proposed by W.G. Johanson et al. in 1972, which include:

- - purulent sputum;
- pathogenic cultures; in cultures of sputum or blood;
- fever 38 ° C or hypothermia 36 ° C;
- leukocytosis 12-10 - or: leukopenia 3.5-109, shift of the leukocyte formula to the left (10% stab or any number of young forms);
- the appearance of fresh focal-infiltrative changes during X-ray examination of the lungs.

Table 1

Independent risk factors for VAP *

Risk factors associated with the patient's condition	Risk factors associated with ongoing treatment
Albumin level <22 g / l	H2 blockers ± anthocides
Age> 60 years	Relaxants
ARDS	Long-term sedation
COPD	Massive blood transfusions
Coma, impaired consciousness	ICP monitoring
Burns, trauma	Mechanical ventilation for more than 2
Multiple organ failure	days
The severity of the underlying disease	PEEP
Massive aspiration of gastric contents	Frequent breathing circuit changes

Colonization of the stomach and increase in pH Colonization of the upper respiratory tract Sinusitis	Reintubation Nasogastric tube Supine position Transportation outside the intensive care unit Previous antibiotic therapy or no antibiotic therapy

Note:*- по J.Chastre и J.Y. Fagon [8].

The diagnosis of pneumonia is made when there is an infiltrate on the chest radiograph in combination with any 3 of the 4 remaining signs [17].

The CPIS (Clinical Pulmonary Infection Score) scale is widely used to objectify the assessment of clinical, laboratory and radiological data in patients with suspected VAP (Table 2).

Table 2

Clinical Lung Infection Scale (CPIS) Scoring

Index	Number of points
Temperature	
>36,5 °C or <38,4 °C	0
>38,5 °C or <38,9 °C	1
>39,0 °C or <36,0>°C	2
The number of blood leukocytes (in mm3)	
>4000 or <11000	0
<4000 or >11000	1 + 1 (in the presence of young forms> 50%)
Index	Number of points
Tracheal secret	
Lack of tracheal secretions	0
The presence of non-purulent tracheal secretions	1

The presence of a purulent tracheal secretion	2
Oxygenation (PaO2 / FiO2, mm Hg)	
> 240 or the presence of ARDS (ARDS is diagnosed with a PaO2 / FiO2 ratio <200 or with a pulmonary artery wedge pressure <18 mmHg and acute bilateral foci of infiltration)	0
<240 and no ARDS	2
Chest X-ray	
No infiltrates	0
Diffuse infiltrate	1
Delimited infiltration	2
Progression of infiltrates in the lungs	
Lack of radiographic progression	0
Radiographic progression (after ruling out acute ARDS and congestive heart failure)	2
Tracheal aspirate culture	
Few pathogenic (predominant) bacteria or no growth	0
Moderate or significant numbers of pathogenic (predominant) bacteria	1 + 1 (in the presence of similar bacteria with Gram stain)

Note. Evaluation of the results obtained: 6 points or more indicates the presence of pneumonia.

Since 1991, this scale has been used in pulmonary practice, then it was adapted for use in ICU in patients with suspected VAP. It is interesting that the violation of gas exchange is one of the diagnostic signs of an infectious "process in. lungs, provided there is no ARDS. In practice, it is rather difficult to use such recommendations, since it is difficult to absolutely reliably determine the cause of the violation of gas exchange.

The GPIS scale can also be used to monitor the dynamics of the patient's condition during treatment and to make decisions about the need to change or the possibility of stopping ABT. The modified CPIS score <6 is an objective criterion for selecting a group of patients with a low risk of bacterial HP. However, some experts in the field of VAP do not see significant, advantages when using CPIS in comparison with other diagnostic approaches [18].

Many experimental and clinical studies use the diagnostic approach outlined by the Centers for Disease Control and Prevention (CDC) guidelines; published in 1997 [19].

CDC guidelines are clinical; radiological and laboratory signs of the disease, summarized in the following groups:

— 1. Clinical:

— an increase in body temperature> 38°C or (much less often) hypothermia <36°0;

— identification of percussion and auscultatory data characteristic of pneumonia;

— the appearance of purulent discharge during TBD sanitation.

— 2. X-ray:

— the appearance of new or progression of previously existing infiltrates, the rapid formation of cavities in the lungs (with the exclusion of pulmonary tuberculosis and oncological pathology).

3. 3. Laboratory:

— leukocytosis> 11-109 / l or leukopenia <4-109 / l;

— the presence of more than 5% of cells with phagocytosed microbial bodies or fragments of microbial bodies in the BALF;

— decrease in PaO_2 (in the absence of other reasons).

4. 4. Microbiological:

— detection of more than 104 CFU / ml in BALF or 103 CFU / ml in aspirate from the trachea, as well as in samples obtained using the "protected brush" method.

5. Histological:

— detection of signs of bronchiolitis, focal bronchopneumonia, confluent bronchopneumonia or lung abscess during microscopy of lung tissue samples. Materials for research can be obtained both during an intravital biopsy (transthoracic or performed through a bronchoscope) and postmortem examination of lung tissue.

For obvious reasons, not all data can be obtained simultaneously, the accuracy of the diagnostic approach without the results of instrumental studies is not known (microscopy, histology, microbiology).

From the point of view of prognosis and determination of treatment tactics, it is important to assess the severity of pneumonia. The criteria for a severe course of hospital pneumonia are:

— respiratory failure, defined as the need for artificial ventilation of the lungs or as the need for an oxygen content in the inhaled air of more than 35% to ensure the saturation of arterial blood with oxygen over 90%;

— rapid progression of radiological changes, multifocal pneumonia or the formation of decay cavities in the pulmonary infiltrate;

— data on the presence of severe sepsis, accompanied by hypotension and / or dysfunction of organ systems;

— shock (systolic blood pressure below 90 mm Hg or diastolic blood pressure below 60 mm Hg);

— the need for the introduction of vasopressor drugs for more than 4 hours;

— diuresis less than 20 ml / h or total urine flow less than 80 ml in 4 hours (if other methods of its determination are not possible);

acute renal failure requiring dialysis [20].

The purpose of developing the presented criteria is to determine the need for urgent correction of antibiotic therapy. The severity of respiratory failure according to the proposed criteria actually corresponds to ARDS.

Severity criteria for community-acquired pneumonia of the British Thoracic Society (impaired consciousness, respiratory rate over 30, urea over 7 mmol / L,

decrease in systolic blood pressure below 90 mm Hg or diastolic blood pressure below 60 mm Hg, age over 65 years) or the pneumonia severity index, which is more difficult to calculate, was also developed to determine the tactics of antibiotic therapy, as well as to assess the need for hospitalization of a patient in a hospital or an intensive care unit [21, 22].

The very fact that there are several recommendations for the diagnosis of HP indicates their imperfection and the need to strengthen approaches to clinical diagnosis by introducing additional objective criteria. It can also be stated that there is a lack of unified approaches to assessing the severity of pneumonia, which partly complicates the assessment of the effectiveness of treatment, including respiratory support.

Methods for sampling material for microbiological diagnostics. The reliability of the diagnosis increases markedly with the use of special methods of microbiological diagnostics, the purpose of which is to clarify the diagnosis of pneumonia as such, as well as to identify potential pathogens.

— Today there is a large arsenal of various methods of microbiological diagnostics, namely: examination of lung tissue (percutaneous lung puncture, transbronchial biopsy), unprotected samples (bronchoalveolar lavage - BAL, unprotected bronchial samples taken blindly), method of protected sampling (protected brush for the collection of the test material, endoscopic BAL, protected bronchoalveolar lavage blind, etc.).

— - The material for culture should be sent to the laboratory within an hour to determine the pathogens and their resistance to antibiotics. The indicator, allowing to differentiate colonization and the infectious process, depends on the method of sampling and varies in the range of 103-105 CFU / ml. In order to increase the reliability of the result, microscopy is used, which makes it possible with a high percentage of probability to determine the reliability of the origin of the collected material in BAL fluid (the number of neutrophils, alveolar macrophages, epithelial cells, the presence of elastic fibers, etc.). In addition, a Gram smear is stained, which makes it possible to purposefully draw up a

treatment regimen if the patient's condition does not allow waiting for the results of a bacteriological culture study.

X-ray diagnostics. Currently, radiography is still an obligatory component of the diagnosis of pneumonia in patients undergoing IV L, although, like the clinical criteria of VAL in general, the sensitivity and specificity of radiography for the diagnosis of pneumonia are not high enough. It has been shown that at the initial stage of the disease in surgical patients, 26% of the opacities detected by CT were not visible on radiography [23].

In addition, asymmetric pulmonary infiltrates consistent with VAP can be caused by a variety of non-infectious causes, including atelectasis, chemical pulmonitis, asymmetric cardiac pulmonary edema, pulmonary embolism, pulmonary contusion, pulmonary hemorrhage, antibiotic response, and asymmetric ARDS. In general, the radiographic specificity of pulmonary tissue opacities for pneumonia is only about 27–35% [24, 25].

It should, however; note that certain radiological features are highly specific and can be extremely helpful in making a diagnosis of pneumonia. Based on several studies, including the pathological study of RGWunderink et al., It has been shown that such radiological signs as the rapid formation of cavities in the area of pulmonary infiltrate (especially if the process progresses) and air bronchography (especially if it is asymmetric) make it possible to make a diagnosis with a high probability pneumonia [25].

Unfortunately, such radiographic manifestations are not common. On the other hand, with the development of ARDS and the presence of diffuse bilateral infiltrates, no additional X-ray signs (however, as well as clinical ones) were revealed, which make it possible to talk about the development of VAP with a high degree of probability. This is a significant problem, since in ARDS, as well as in pneumonia, signs of an inflammatory reaction are expressed, and it is extremely difficult to make a differential diagnosis in this situation. The situation is even more complicated when pneumonia itself becomes the cause of the development of ARDS.

There is no agreed position regarding the location of magnetic resonance imaging and computed tomography. With all their advantages in relation to the diagnostic value, doubts are raised by the problematic nature of the organization of studies in patients with pronounced disorders of gas exchange [9].

Postmortem diagnosis of VAP. For 15 years from the mid-80s to the end of the 90s. histopathological conclusions were recognized as almost indisputable in the diagnosis of VAP [18, 26, 27, 28, 29, 30].

Perhaps, this method still remains the most reliable criterion in controversial issues about the presence of VAP in a patient, however, it is referred to the "gold standards" of diagnosis less and less. From a pathohistological point of view, VAP represents foci of lung tissue compaction with intensive accumulation of leukocytes in the bronchioles and in the adjacent alveoli [31, 30, 32].

This definition of pneumonia does not take into account the severity and prevalence of the disease. For a more complete description of pneumonia, there are [33]:

— lobar (croupous) pneumonia, in the development of which 4 successive stages can be distinguished: tide, red and gray hepatization, resolution. A classic example of this pneumonia is pneumococcal pneumonia.

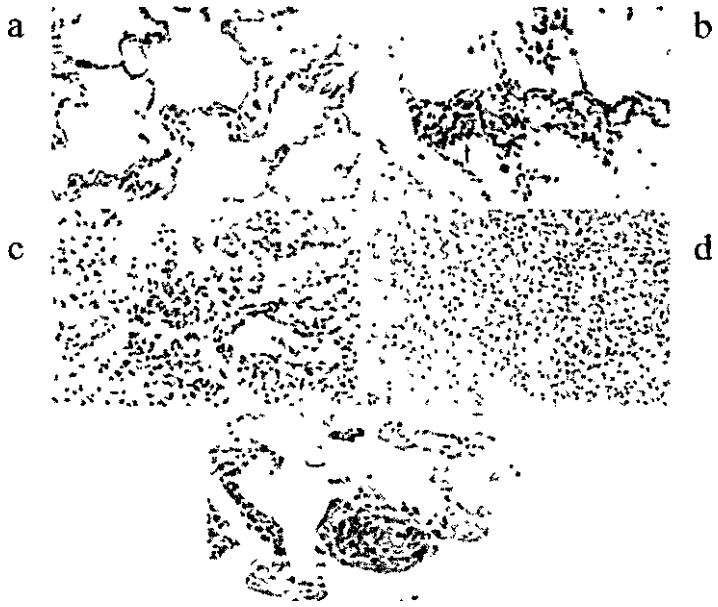
— bronchopneumonia, in which lobular, catarrhal and focal pneumonia is released. Unlike croupous pneumonia, in which the infectious process proceeds according to the aerogenic variant, with bronchopneumonia, the bronchial wall is first affected and only secondarily - per continuitatem - pulmonary parenchyma due to the defeat of the alveoli adjacent to the terminal bronchioles;

— interstitial pneumonia, which is usually caused by viruses and less often mycoplasma.

A number of studies carried out in recent years have used slightly different VAP criteria. So, for example, S.N. Marquette et al. [27] define VAP as compaction of lung tissue at the level of secondary lobules in combination with an intensive accumulation of polymorphic cell leukocytes, fibrinous exudate, and fragmented cellular elements within the lumen of the alveoli. By lung abscess,

they mean pneumonia associated with tissue necrosis and gross damage to the lung structure.

N. Fabregas et al. [26] distinguish 4 stages of VAL development (Fig. 1): a) early stage (0-2 days) - stagnation of blood in the pulmonary capillaries with an increase in the number of polymorphic cell leukocytes; b) an intermediate stage (3-4 days of illness) - the presence of fibrin, a small number of erythrocytes and polymorphic cell leukocytes in the lumen of the alveoli; c) advanced stage of VAL (from 5 to 7 days) - polymorphic cell leukocytes fill a significant part of the volume of the alveoli, macrophages with phagocytosed and fragmented cellular elements are detected; d) the stage of reverse development (> 7 days) - the inflammatory exudate from the alveoli begins to disappear due to active phagocytosis by mononuclear cells.



Rice. 1. Normal pulmonary parenchyma (a) and stages of pneumonia (staining with hematoxylin and eosin x 200). Early stage (b), intermediate stage (c), advanced stage (d) and reverse development stage (e) e

It is also necessary to dwell on the criteria proposed by J.W.D. Johanson et al. for the diagnosis and determination of the severity of VAP [17].

On the basis of experimental studies, they identified mild, moderate and severe forms of bronchopneumonia. The mild form is defined as the presence of diffuse neutrophilic infiltrates localized in the terminal bronchioles and adjacent

alveoli. Moderate pneumonia is defined as the spread of a mild form with the formation of larger confluent foci between adjacent lobules. In the lumen of the bronchioles, purulent discharge is often present. A severe form of pneumonia is characterized by the formation of even larger foci, which can even be determined macroscopically and are usually associated with tissue necrosis. A similar classification is described in J.J. Rouby et al. [34].

They distinguish the following degrees of severity of VAP:

- bronchiolitis;
- focal bronchopneumonia;
- drain bronchopneumonia;
- drain bronchopneumonia, lung abscess.

In 1992 J.J. Rouby et al. published the results of the study obtained in the pathological study of patients with VAP [28].

It turned out that pneumonia tends to be localized in the parts of the lungs located at the lowest point of the chest (depending on the prevailing position of the patient's body during mechanical ventilation). This finding makes it possible to assume the influence of gravitational forces on the predominant damage to certain parts of the lungs. Bronchopneumonic lesions were usually small in size and scattered. There were foci of pneumonia at various stages of development, which made it possible to think about the prolongation of the infection processes in time, the possibility of reinfection. In addition, it was found that the foci were often interspersed with pathologically altered areas of the lungs without signs of bacterial damage. Up to one third of lung tissue samples with histological signs of pneumonia during microbiological examination were sterile, 45% of samples had a concentration of microorganisms below the critical diagnostic level (103 CFU / ml).

Similar results were obtained by N. Fabregas et al., Who performed simultaneously histological and microbiological analysis of 375 samples of lung tissue obtained from 25 deceased patients with a diagnosis of upper urinary tract infection [26].

Interestingly, these authors described the frequent detection of pathogenic microorganisms above the diagnostic level in the study of the lung; tissue with no histological signs of pneumonia at all. Since the autopsies in this study were carried out no later than 30 minutes after the onset of death, it is not possible to assume postmortem contamination of the lung tissue. As a result, it was concluded that the growth rate of microorganisms obtained in postmortem lung tissue samples does not correlate well with the severity of damage to the tissue structure of the lungs. These findings contradict one of the well-established dogmas in approaches to the diagnosis of VAP: histological and microbiological examination of lung tissue are the two5 most important criteria in confirming this diagnosis, and the simultaneous detection of these two signs is the standard for verification of pneumonia [35].

It is important that the data of J.J. Rouby et al. applied not only to patients receiving intensive antibiotic therapy in the ICU, but also to patients who were not injected with antibacterial drugs. The absence of a significant correlation between the severity of histological damage to lung tissue and the number of microorganisms obtained from these samples during microbiological examination was also noted in the work of S.N. Marquette et al. [27].

Commenting on these observations, it can be assumed that the severity of a patient's condition with VAP does not in all situations depend only on the degree of infection with TBD and lung tissue. Apparently, no less important are the individual characteristics of the human body, including the activity of the natural system of antimicrobial defense of the lungs, as well as the specificity of the pathogen itself (for example, the presence of toxins).

What is the sensitivity and specificity of intravital methods; diagnostics of VAL compared with histological data. Works on this problem are not too numerous, and their results are contradictory. For example, in the works of A. Torres et al., S.H. Kirtland et al. [36; 29] was discovered; weak correlation; the relationship between the clinical diagnostic criteria of VAL and the results of a combined histological study of postmortem lung tissue samples. CIPS proposed by

J. Pugin et al. had the following indicators of sensitivity: 72, 77, 100% and specificity: 85, 42 and 69% [37 18, 38].

Assessment of the diagnostic significance of various clinical criteria is complicated by the fact that it is not known how reliable the results of histological examination are themselves, and whether they can be used as a reference. D.E. Corley et al. published a paper on this issue [31].

Differences in the assessment of histological preparations of lung tissue; four pathologists; participating in the study on WATT, occurred in 18-38% of cases. When pathologists were introduced to the criteria for histological diagnosis of VAP, J.R. Johanson et al. and asked to be strictly guided by them in their estimates, the detection rate of pneumonia increased by 13%.

Summarizing the above data, it should be concluded that the data of postmortem histological examination are; is currently the most reliable method in the diagnosis of VAP, but this method also has certain limitations and needs standardization of approaches when making a conclusion about the presence of the disease.

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