Review Article

Preanalytical phase in pleural fluid analysis

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Abstract: The total testing process for pleural fluid samples comprises a continuum of five phases, from the initial procedures of the pre-preanalytical phase to the final steps in the post-postanalytical phase. It can be assumed that the extra-analytical phases in laboratory testing of pleural fluid samples are equally susceptible to errors and that the error rate is comparable to (or even higher than) the corresponding phases in standard samples analysis. It is through harmonization of the preanalytical phase that the risk of errors might be reduced and patients' safety improved. However, with the exception of a few documents from standard writing bodies and national societies, little evidence is available on harmonization of the preanalytical phase for pleural fluid testing. A thorough understanding of potential errors in the preanalytical phase of pleural fluid analysis enables laboratory professionals to ensure reliable testing results and to assist clinicians in the diagnostic evaluation of pleural effusion. In this review, we discuss the preanalytical phase of pleural fluid analysis, presenting variables potentially affecting the quality of pleural fluid samples and hence the analytical reliability of pleural fluid analysis.

Keywords: Pleural fluid; preanalytical phase; laboratory testing; patient safety

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Introduction

Pleural fluid is physiologically present in the pleural space in small amounts. It is continuously produced through plasma ultrafiltration and then normally reabsorbed *via* the lymphatic vessels and venules of the pleura. The presence of systemic and localized disorders that affect the balance between fluid formation and reabsorption results in fluid accumulation, called a pleural effusion. The most common causes of pleural effusions are heart failure, pneumonia, malignancy etc. (1,2).

The clinical evaluation of a patient presenting with pleural effusion comprises the patient history, physical examination and radiological or/and ultrasound studies or computed tomography chest scans. Laboratory testing of pleural effusions is indicated in cases without no evident underlying diagnosis and provides useful information for the determination of the pleural fluid's aetiology. The use of laboratory tests enables the differentiation of pleural effusions into transudates and exudates, which greatly simplifies the diagnostic process and reduces the need for further unnecessary testing. Additionally, in cases of exudative effusions, when additional testing is indispensable in order to establish a definite diagnosis, specific laboratory tests are essential in elucidating the cause of fluid accumulation (2,3).

As for standard (e.g., blood) samples, the total testing process for pleural fluid samples comprises a continuum of five phases, from the initial procedures of the pre-preanalytical phase to the final steps in the post-postanalytical phase (4). It is now well accepted and documented that the extra-analytical phases for standard samples are more vulnerable to errors; however, such specific evidence (i.e., error rates) for pleural fluid samples

is lacking (5,6). Still, it is reasonable to assume that the extra-analytical phases in laboratory testing of pleural fluid samples are equally susceptible to errors and that the error rate is comparable to (or even higher than) the corresponding phases in standard samples analysis (7).

For years now, the Working group for Preanalytical Phase (WG-PRE) of the European Federation for Clinical Chemistry and Laboratory Medicine (EFLM) is dedicated to the pursuit of quality and harmony in the preanalytical phase of laboratory testing. It is through harmonization of the preanalytical phase that the risk of errors might be reduced and patients' safety improved (8). However, with the exception of a few documents from standard writing bodies and national societies, little evidence is available on harmonization of the preanalytical phase for pleural fluid testing (9-12).

Collection and handling of a pleural fluid sample until analysis greatly affects the quality of such sample and in turn might affect the reliability of pleural fluid test results and ultimately patient safety. Thereby preanalytical variables similar to those influencing standard fluid analysis might adversely affect pleural fluid laboratory testing. In this review, we discuss the preanalytical phase of pleural fluid analysis, present variables potentially affecting the quality of pleural fluid samples and hence the analytical reliability of pleural fluid analysis. Furthermore, we suggest the most appropriate conditions for collection, transport and processing of pleural fluid samples in order to minimize preanalytical errors in this field of laboratory analysis.

Test ordering in pleural fluid analysis

The preanalytical phase of pleural fluid laboratory testing starts with test requesting: the right test should be ordered in the right time for the right patient (6). Pleural fluid samples sent to the laboratory should be accompanied with a test request form or its electronic equivalent. These should adhere to ISO 15149 requirements, including as much identification information on the patient, sample type and the ordering clinician. Additionally, the collection site and anatomic origin of the pleural sample should be stated, together with any information on therapy (11,13,14). Of note, diuretic therapy tends to concentrate pleural effusions, which consequently might lead to an erroneous classification of the fluid as exudate because of measured higher proteins and lactate dehydrogenase (15).

Pleural fluid analysis is widely available and relatively inexpensive since performed using automated biochemical and haematology analysers. However, the appropriateness of test ordering is not well defined and is less consistent in this area of laboratory testing. A rational approach to an efficient and cost-effective test ordering in pleural fluid analysis should include the adoption of diagnostic algorithms, designed by laboratory professionals and clinicians, in order to maximize the usefulness of the obtained test results in patient management (2).

Pleural fluid samples are collected by an invasive collection procedure that puts the patient at risk of various complications and (as opposed to venous blood sampling) recollection is not feasible (3,11). Therefore, the inappropriate use of laboratory tests (i.e., over-testing, unusual testing) on these precious samples is an issue that needs to be addressed. Laboratory workout of pleural fluid samples should include only tests with established clinical utility, preferably selected in collaboration with the clinician. Since often a multitude of tests are requested from a single pleural fluid sample, care should be taken not to waste the sample on tests that will not produce useful diagnostic information (3,9,11). Ample evidence is available in the literature on the diagnostic utility of individual laboratory tests in pleural fluid analysis and will not be described here in further detail (9,11,16)

Pleural fluid sample collection

Pleural fluid samples are collected using a procedure called thoracentesis (or pleural aspiration), indicated for therapeutic and/or diagnostic purposes. Diagnostic thoracentesis entails needle aspiration of pleural fluid from the pleural space and is usually performed at the bedside (clinical wards, emergency or operating rooms) by trained clinicians (17,18). Thoracentesis is not under direct laboratory supervision and variations in collecting practices might result in various preanalytical errors potentially affecting the quality of pleural fluid samples test results and patients management. Accurate identification of the patient and labelling of collection containers is crucial, and should be performed similarly to standard fluid collection procedures (14). Additionally, potentially erroneous practices pertaining to the collection procedure should be avoided. For example, it was suggested that local anaesthetics used to alleviate pain in patients undergoing thoracentesis might be injected in small amounts in the pleural space and contaminate the collected pleural fluid sample. Apart from its dilution effect potentially affecting glucose determinations, the anaesthetic might falsely lower

the fluid's pH (especially in small effusions) and thus affect patient management (19,20). Furthermore, syringes and needles used to inject local anaesthetic should not be used to collect pleural fluid samples (21,22). Finally, it has been reported that pleural fluid pH might depend on sampling location, i.e., that pH might display clinically important variations between different locules in complicated parapneumonic effusions (23). In order to standardize the collection procedure and minimize the occurrence of potential errors, available clinical practice guidelines should be followed and local standard operating procedures (including laboratory instructions) instituted (24).

Acceptable volumes of pleural fluid sample should be submitted for analysis and minimum sample volumes defined in each individual laboratory. Usually, a total pleural fluid sample volume of 30 mL is sufficient to perform complete biochemical, cytological and microbiological investigations (20). Occasionally, the volume of the submitted sample will be insufficient to allow the performance of all tests requested. In such cases, the selection of what tests to prioritize is best brought in collaboration with the treating clinician and in conjunction with the clinical context (2,3,11).

No specific requirements for patient preparation and time of collection are applicable for pleural fluid laboratory testing.

Pleural fluid collection containers

After thoracentesis, the pleural fluid collected is immediately transferred into appropriate containers. This preanalytical step is particularly important and error prone. Containers should be appropriately labelled before or immediately after thoracentesis but in the presence of the patient, in order to reduce the risk of unlabelled or incorrectly identified containers. At least two unique identifiers (e.g., name and date of birth) should be used to identify the container. Due to the complexity pertaining pleural fluid collection, unlabelled or not properly labelled containers should not be rejected immediately, but efforts should be undertaken (in close communication with the clinician) to unequivocally link the submitted sample to the right patient (11,14).

The containers used for pleural fluid analysis are dictated by the tests ordered (25). The container of choice to use for biochemical analysis of pleural fluid samples is a heparin anticoagulated tube, although plain tubes (containing no additives) are also acceptable. Glucose might be collected in tubes containing a glycolysis inhibitor. The minimal volume of pleural fluid sample for biochemical analysis is 3 mL (11,15,20,24). Pleural fluid samples for cell counts should be distributed in ethylenediaminetetraacetic acid (EDTA) containing tubes in order to avoid clotting and cell clumping. This was demonstrated in an investigation performed by Conner *et al.* They showed that white blood cell counts obtained from plain tubes with an automated analyser were about 50% lower compared to those obtained from EDTA tubes, and attributed the difference to cell clumping (26). The minimal recommended volume for cell counts determination is 3 mL (11,20). Similar to best practice for standard samples and in compliance to manufacturer's instructions, additive containing tubes should be mixed gently in order to ensure proper mixing and avoid sample clotting (3,11,20).

If pleural fluid pH measurement is requested from the laboratory, the acceptable consensus practice in the literature is to collect samples anaerobically in syringes containing lyophilized, balanced lithium heparin (3,11). However, it has been demonstrated that the indirect collection of pleural fluid samples for pH measurement (i.e., collection of pleural fluid samples in large un-heparinised syringes followed by sample transfer to a blood gas syringe) does not impact clinical decisions and patient management. This might be an acceptable time-saving practice for the clinician performing thoracentesis, concomitantly reducing the risk of complications during this procedure, but only under the assumption that any exposure of the sample to room air is avoided (19,21,27). Prolonged exposure to air produces clinically significant changes in pleural fluid pH and should be avoided (19).

In the absence of appropriate reference ranges for analytes measured in pleural fluid samples, the appropriate interpretation of pleural fluid laboratory testing results is enabled by concomitantly collecting a serum sample (11). It is generally accepted that a serum sample for interpretation purposes should be collected within 1 hour from pleural fluid collection, although this issue has not been entirely clarified yet (10,11,24). For example, an investigation on pleural and ascitic fluid samples suggested that interpretation of Light's criteria was not jeopardized if serum samples were collected within 2 hours (28).

Pleural fluid transport and sample processing

Since data on the stability of pleural fluid samples after collection are rather scarce, the accepted consensus is that pleural fluid samples should be transported to

the laboratory promptly after thoracentesis at room temperature (11,20). After positive identification, the samples should be processed immediately upon receipt. Pleural fluid samples for biochemical analysis should be centrifuged before analysis according to serum centrifugation conditions (9,11,15).

If pleural fluid analysis is delayed, samples might be appropriately stored. The stability of clinically relevant chemistry analytes in pleural fluid samples under different storage conditions prior to analysis was recently investigated. The results showed that if pleural fluid samples are collected in plain (no additive) tubes and centrifuged upon receipt in the laboratory, total proteins, albumin, lactate dehydrogenase, cholesterol, triglycerides, creatinine, urea, glucose and amylase are stable for up to 6 hours if stored at room temperature. Furthermore, all the analytes investigated are stable up to 30 days if stored at –20 ℃, except for lactate dehydrogenase and glucose. Pleural fluid glucose is stable for up to 3 days at –20 ℃, while lactate dehydrogenase should not be preserved frozen in pleural fluid samples due to its compromised stability (29). The stability of glucose in pleural fluid samples collected in tubes containing oxalate is 24 hours at room temperature (20). In cases of delayed cytological examination the cell integrity in pleural fluid samples might be maintained for up to 48 hours if samples are stored refrigerated (3,30). For cell counts a 24-h delay in analysis is acceptable if pleural fluid samples are collected in EDTA tubes and stored at 4 ℃ (25). Pleural fluid samples for pH determination, if collected in commercially available syringes for blood gas analysis, might be stored for up to 1 hour at room temperature without producing substantial clinically significant alterations in pH values (19,21,31).

Pleural fluid adenosine deaminase (ADA) is routinely used to diagnose tuberculous pleural effusions. At room temperatures ADA activities decrease gradually over time. Miller *et al.* demonstrated that the addition of 5% glycerol and 5% ethylene glycol resulted in the stabilization of the enzyme in pleural fluid samples for at least 20 days at both room temperature and at 37 ℃, and for at least 10 days at otherwise denaturing temperature of 45 ℃. In practice this might be used if shipment of pleural fluid samples for ADA determination to distant laboratories is needed (32). Antonangelo *et al.* investigated the stability of ADA in 27 pleural fluid samples collected in EDTA tubes when supernatants were stored up to 28 days at 4 ℃ or –20 ℃. The stability of ADA was not compromised in either storage conditions for up to 28 days (33). Although preliminary results showed that N-terminal pro-brain natriuretic peptide (NT-proBNP) might be stored for up to 1 month at –70 ℃, the stability of other "non-routine" analytes in pleural fluid samples (e.g., procalcitonin, tumour markers and NT-proBNP) has not yet been appropriately investigated (11,34). Thus, laboratories should investigate the stability of relevant pleural fluid analytes in order to determine the storage period in which delayed, additional testing or retesting is feasible (11).

Interferences

The composition of pleural effusions differs greatly from the composition of standard samples analysed in the laboratory. This is called the matrix effect and refers to differences in pH, electrolytes, proteins and lipid concentrations found in pleural fluid samples which might be marked. This influences the change in physical and chemical properties of the pleural fluid and might affect the preanalytical and analytical phase of analysis (9). Specifically, due to the matrix effect, pleural fluid samples might present with altered fluid tension, viscosity and/or miscibility which in turn might affect the accuracy of sample aspiration and dispensing, the mixing or cleansing of the dispensing and reaction mechanisms. These alterations are usually not recognized by the analytical system used and might jeopardize the reliability of the measurement. This issue is prevailed by validating and/or verifying the assays used for pleural fluid analysis in each individual laboratory (9,11). A preliminary investigation showed that the matrix effect does not impact significantly pleural fluid measurements (35). However, pleural fluid samples should be at least visually inspected for altered quality before analysis in order to avoid instrument failures and/or measurement errors (2,9,11).

The literature consensus is that extremely bloody, turbid or purulent pleural fluid samples, and pleural fluid samples with pronounced clotting tendency are not suitable for analysis (11,15,19). However, the possible impact of lower grade haemolysis, icterus and/or lipemia present in pleural fluid samples should be addressed. In a recent retrospective investigation of laboratory data on 3,000 body fluid samples (including pleural fluid), the prevalence of haemolysis, icterus and lipemia and their possible impact on results reliability was evaluated (36). The criteria used for body fluid interference indices were identical to those applied for serum/plasma interference index limits as per manufacturer's declaration. Although the general

distribution of interference indices in body fluid samples was similar to serum/plasma samples, a higher proportion of body fluid samples with severe icterus or lipemia was found. Compared to other body fluids, pleural fluid samples more frequently exceeded the limits of haemolysis interference index due to the frequent request for lactate dehydrogenase determination which has a relatively low haemolysis index. In fact, lactate dehydrogenase was the analyte most commonly affected by all interferences, which has important implications in pleural fluid laboratory testing since it is one of the cornerstones in differentiation of transudates and exudates by Light's criteria (35). Results from an individual validation report of multiple body fluid tests and body fluid types showed that serum interference indices set by the manufacturer are not transferable to pleural fluid samples (37). Consequently, validation studies should be performed by each individual laboratory in order to establish analyte specific interference limits for pleural fluid samples.

Conclusions

Taking into account the unique nature of pleural fluid samples and the relatively low frequency of their laboratory analysis, the role of laboratory professionals is of utmost importance in this field. A thorough understanding of potential errors in the preanalytical phase of pleural fluid analysis enables the laboratory to produce reliable testing results. Furthermore, laboratory professionals should assist clinicians in the diagnostic evaluation of pleural effusion, especially regarding test selection and test prioritization. Finally, laboratory professionals should raise awareness of the need to harmonize the preanalytical phase of pleural fluid laboratory testing by encouraging the use of appropriate preanalytical procedures in order to reduce the risk of preanalytical errors and ensure high quality test results.

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