The Rational Clinical Examination

Does This Patient Have an Exudative Pleural Effusion?
The Rational Clinical Examination Systematic Review

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IMPORTANCE Thoracentesis is performed to identify the cause of a pleural effusion. Although generally safe, thoracentesis may be complicated by transient hypoxemia, bleeding, patient discomfort, reexpansion pulmonary edema, and pneumothorax.

OBJECTIVE To identify the best means for differentiating between transudative and exudative effusions and also to identify thoracentesis techniques for minimizing the risk of complications by performing a systematic review the evidence.

DATA SOURCES We searched The Cochrane Library, MEDLINE, and Embase from inception to February 2014 to identify relevant studies.

STUDY SELECTION We included randomized and observational studies of adult patients undergoing thoracentesis that examined diagnostic tests for differentiating exudates from transudates and evaluated thoracentesis techniques associated with a successful procedure with minimal complications.

DATA EXTRACTION AND SYNTHESIS Two investigators independently appraised study quality and extracted data from studies of laboratory diagnosis of pleural effusion for calculation of likelihood ratios (LRs; n = 48 studies) and factors affecting adverse event rates (n = 37 studies).

RESULTS The diagnosis of an exudate was most accurate if cholesterol in the pleural fluid was greater than 55 mg/dL (LR range, 7.1-250), lactate dehydrogenase (LDH) was greater than 200 U/L (LR, 18; 95% CI, 6.8-46), or the ratio of pleural fluid cholesterol to serum cholesterol was greater than 0.3 (LR, 14; 95% CI, 5.5-38). A diagnosis of exudate was less likely when all Light's criteria (a ratio of pleural fluid protein to serum protein >0.5, a ratio of pleural fluid LDH to serum LDH >0.6, or pleural fluid LDH >two-thirds the upper limit of normal for serum LDH) were absent (LR, 0.04; 95% CI, 0.02-0.11). The most common complication of thoracentesis was pneumothorax, which occurred in 6.0% of cases (95% CI, 4.0%-7.0%). Chest tube placement was required in 2.0% of procedures (95% CI, 0.99%-2.9%) in which a patient was determined to have radiographic evidence of a pneumothorax. With ultrasound, a radiologist's marking the needle insertion site was not associated with decreased pneumothorax events (skin marking vs no skin marking odds ratio [OR], 0.37; 95% CI, 0.08-1.7). Use of ultrasound by any experienced practitioner also was not associated with decreased pneumothorax events (OR, 0.55; 95% CI, 0.06-5.3).

CONCLUSIONS AND RELEVANCE Light's criteria, cholesterol and pleural fluid LDH levels, and the pleural fluid cholesterol-to-serum ratio are the most accurate diagnostic indicators for pleural exudates. Ultrasound skin marking by a radiologist or ultrasound-guided thoracentesis were not associated with a decrease in pneumothorax events.

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Clinical Scenario

A 74-year-old man is admitted to the hospital for cough, dyspnea, and fever. He has a history of congestive heart failure, a temperature of 39°C, respiratory rate of 26/min, oxygen saturation of 86% on ambient air, decreased breath sounds, dullness to percussion in the left lower thorax, and a white blood cell count of 19 600/μL. Chest radiography shows opacification of the left hemithorax consistent with a pleural effusion. A thoracentesis is planned to distinguish between an exudative and transudative effusion because the causes and management of pleural effusions differ when they are transudates vs exudates; for example, the effusion in this patient could be from heart failure or a parapneumonic process. The appropriate tests of the fluid must be ordered to establish the diagnosis and also to determine the techniques that best ensure procedural success with minimal complications.

Importance of a Diagnostic Thoracentesis

Pleural effusions are an accumulation of fluid in the pleural space from pulmonary, pleural, or extrapulmonary diseases. Information from the patient's medical history and physical examination can help differentiate between transudative and exudative effusions, but the distinction between the 2 types can only be established by direct examination of the pleural fluid.[1] Light's criteria are often used to establish a diagnosis of exudative effusion.[2] An exudate is present when at least 1 of the following is observed: a ratio of pleural fluid protein to serum protein greater than 0.5; a ratio of pleural fluid lactate dehydrogenase (LDH) to serum LDH greater than 0.6; or pleural fluid LDH greater than two-thirds the upper limit of normal for serum LDH (previously, a cutoff value of 200 U/L was used).[2] When Light's criteria are used,[3-7] 7.8% to 15% of effusions are incorrectly classified as exudates when they are really transudates, as defined by a microbiological or pathological diagnosis (eg, malignant cells or specific organism in pleural fluid) or clinical response to treatment (eg, resolution with diuresis).

Adverse Events Associated With Thoracentesis

Thoracentesis is an invasive procedure that is associated with complications including puncture site pain, pneumothorax, bleeding (eg, hematoma, laceration of intercostal artery, and liver or spleen puncture), transient hypoxemia, reexpansion pulmonary edema, vasovagal events, malignant seeding of the needle tract, and adverse reactions related to anesthetic or topical antiseptic solutions used during the procedure.[8-10] Although uncommon, intrapleural retention of catheter fragments can also occur.[11] Pneumothorax is the most important complication and occurs in approximately 1.3% to 26% of procedures.[12] Observational studies suggest that the technique used for thoracentesis influences the types and frequency of subsequent complications. It is generally believed that ultrasound guidance decreases the risk of pneumothorax.[13,14]

Little is known about the safety of thoracentesis in patients with coagulation abnormalities such as prolonged prothrombin time, prolonged partial thromboplastin time, or thrombocytopenia. One case series showed no increase in bleeding complications associated with thoracentesis among patients with mild elevation of prolonged prothrombin time or prolonged partial thromboplastin time (up to twice the midpoint normal range) or with platelet counts between 50 × 10^3/μL and 99 × 10^3/μL.[15] In a retrospective cohort study (n = 1076), the risk for bleeding was not increased for patients with international normalized ratio greater than 3 (n = 32) or platelet count less than 25 × 10^3/μL (n = 12) when radiologists using ultrasound guidance performed all of the procedures.[16] Patients with elevated baseline creatinine (6-14 mg/dL) may have a greater decline in postprocedural hemoglobin when compared with patients having normal serum creatinine levels.[15] In general, consideration of prophylactic plasma or platelet transfusion before thoracentesis should be individualized but is likely unnecessary.[17]

When patient positioning is not optimal (eg, partially recumbent), liver or spleen puncture may occur. Outcomes from this complication are generally favorable if a small-bore needle is used and if the patient is not receiving anticoagulants or does not have a bleeding diathesis.[18]

Removing too much fluid at thoracentesis may be detrimental. A small case series[19] describes consistent and predictable hypoxemia correlating with increasing volume of pleural fluid extracted (r = 0.57; P < .05). In the same study,[19] all patients underwent thoracentesis using an 18-gauge needle with a syringe connected to a stopcock collection system, enabling different volumes of pleural fluid removal. Rapid removal of large fluid volumes with resultant reexpansion pulmonary edema caused hypoxemia that was easily reversed by low-flow oxygen therapy within 24 hours of the procedure.[20] One proposed means for reducing the risk of large-volume (>1L) thoracentesis-associated hypoxemia is to monitor the pleural fluid pressure by manometry as it is removed; a pleural pressure less than −20 cm H_2O has been suggested to be associated with increased risk of reexpansion pulmonary edema.[21] Two studies suggested that greater total changes in pleural pressure (mean [SD], −20 [10] cm H_2O; range, 5-43) and not the absolute volume of pleural fluid extracted may be associated with an increased risk of reexpansion pulmonary edema.[22,23] In one study,[23] 1 in 4 patients had an end-of-procedure or closing pleural pressure of less than −20 cm H_2O.

Contraindications to Thoracentesis

Thoracentesis may be deferred for patients with severe hemodynamic instability or respiratory compromise not caused by the effusion itself. Patients receiving positive end-expiratory pressure mechanical ventilation do not have increased risk for pneumothorax compared with patients not receiving such therapy.[24-26] When pneumothorax occurred, risks were greater for tension pneumothorax or subsequent development of bronchopleural fistulae.[27-29]

Among patients receiving therapeutic anticoagulation or with a bleeding diathesis (eg, prolonged prothrombin time or prolonged partial thromboplastin time >1.5× the normal range, platelet count <25 × 10^3/μL, or serum creatinine >1.7 mg/dL), reversal of the coagulopathy or thrombocytopenia should be individualized to the clinical scenario when performing thoracentesis.[15,16] For instance, when the procedure is to be performed under ultrasound guidance by an experienced operator, the risk of bleeding is so low that testing or reversal of abnormal coagulation may be unnecessary.[30]

The purpose of this systematic review is to identify which tests optimally distinguish between transudative and exudative effusions and to review thoracentesis complications and their preven-

tion. This study provides a best-practice approach for thoracentesis in adults with pleural effusion based on systematic evidence review and its integration with expert opinion.

Methods

Literature Search Strategy

We searched the Cochrane Library (Wiley interface, February 2014), Medline (OVID interface, 1950 to February 2014), and Embase (OVID interface, 1980 to February 2014) to identify relevant studies (eTable 1 in the Supplement).

Study Selection and Data Extraction

Diagnostic Accuracy Studies

We extracted data on the physical characteristics of the effusion (eg, appearance, viscosity), white and red blood cell counts, and the results of commonly available biochemical tests (eg, pleural protein, albumin, cholesterol). Study quality was summarized using a checklist designed for The Rational Clinical Examination series, in which a threshold of 100 patients included in the study was used to distinguish level 1 from level 2 studies.[31] We included only studies for which primary data or appropriate summary statistics were available (see the Supplement for data extraction process).

We retained studies in which the investigators used a microbiological or pathological result to categorize effusions as exudates or transudates. In these studies, the investigators used their clinical knowledge, without regard to Light's criteria, based on the proven etiology of the effusion. For example, patients with effusions secondary to infection, malignancy, or inflammatory conditions were considered to have exudates, whereas patients with heart failure or nephritic syndrome were considered to have transudates. These studies were considered to have the most reliable data because the diagnosis was established independently of the symptoms, signs, and Light's criteria. Several studies used Light's criteria as the reference standard for classifying effusions, rather than the final diagnosis. Because this approach is a common clinical practice, for comparison purposes we show the results from these studies in the Supplement only since studies that test a component of Light's criteria and then used those criteria as a reference standard will be biased toward higher accuracy.

Studies of Procedural Methods

The search for this review included only randomized and observational studies of adult patients (aged 18 years or older) undergoing interventions intended to reduce the risk of adverse events (eg, patient discomfort, "dry tap" [no fluid obtained], pneumothorax) at the time of thoracentesis. Interventions and factors of interest included puncture apparatus (eg, needle size) and routine postprocedural chest radiography. Attempt was also made to identify studies that assessed the effect of operator experience. The outcomes of interest included success in obtaining pleural fluid, number of attempts, and incidence of pneumothorax occurring up to 7 days after thoracentesis. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) system was used to rate the overall quality of evidence.[32] More specifically, the overall quality of a study was categorized as high (further research is very unlikely to change confidence in the estimate of effect), moderate (further research is likely to have an important effect on confidence in the estimate of effect and may change the estimate), low (further research is very likely to have an important effect on confidence in the estimate of effect and is likely to change the estimate), or very low (any estimate of effect is uncertain).[32]

Statistical Methodology

Sensitivity, specificity, and likelihood ratios (LRs) were calculated for studies of test accuracy.[33] If a study contained any zeros in the 2 × 2 table resulting in LR estimates of zero or infinity, 0.5 was added to all counts for that study. For any findings evaluated in only 2 studies, the range for the odds ratio (OR) or LR without a point estimate or 95% CI is reported. For findings evaluated in at least 3 studies, univariate random-effects summary ORs and LRs were calculated using version 1.4 of Meta-DiSc[34] since bivariate measures were similar or failed to converge on a solution.[35] When test results were evaluated at different threshold levels, the data were abstracted at each level and then the optimum threshold was selected based on a balance between the diagnostic OR and the width of its CI.

Review Manager version 5.0.22 was used to calculate summary adverse event rate, summary risk difference and 95% CIs, and pooled ORs and 95% CIs for adverse outcomes of thoracentesis. If 3 or more studies examined the same adverse outcome, heterogeneity was assessed using the I^2 statistic to determine the percentage of total variability across studies attributable to heterogeneity rather than chance. Heterogeneity was categorized using published guidelines: low (I^2 = 25%-49%), moderate (I^2 = 50%-74%), and high ($I^2 \geq 75\%$).[36] To conduct meta-analyses of the risks of pneumothorax, chest tube placement, dry tap, and hemothorax, the proportion of patients in each study who had each complication was converted to the log OR (ie, summary rate) first.[37] The standard error of each log odds, where odds = X/(n − X), X = number of events, and n = total number of patients, was calculated as the square root of $(1/X + 1/[n - X])$. Natural log-transformed odds were pooled using the generic inverse variance method. When there were enough studies to detect possible publication bias (specifically for the analyses of pneumothorax, chest tube placement, dry tap, and hemothorax), funnel plots (scatterplot of standard error of logOR against logOR for each study) were inspected using the Egger regression test.[38] This study used random-effects models, which incorporate between-trial heterogeneity and generally yield wider CIs when heterogeneity is present.

Results

Accuracy of Interpretation of Results in Diagnosis of Pleural Effusion

A total of 1914 citations were retrieved for accuracy of pleural fluid analysis in diagnosing a pleural effusion as either transudative or exudative. After applying inclusion and exclusion criteria, 48 were retained (eFigure 1, eTable 2, and eTable 3 in the Supplement).[2-6,39-81] Overall, 4 of these studies were classified as level 1, 1 study was classified as level 2, and 43 studies were classified as level 4 on The Rational Clinical Examination quality scale.[31]

Several biochemical tests were assessed to distinguish between transudative and exudative pleural fluid (**Table 1**). Studies of these tests were difficult to summarize since they included patients with different underlying causes for their pleural effusions (eTable 8, eTable 9, eTable 10 in the Supplement). The most valid studies included patients not selected by underlying disease and for whom the final diagnosis of the cause of the pleural effusion was the

Table 1. Diagnostic Accuracy for Most Useful Findings for Diagnosis of Pleural Exudate[a]

Source	Patients, No.	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive LR (95% CI)	I^2, %	Negative LR (95% CI)	I^2, %
Pleural cholesterol >55 mg/dL[5,77], range[b]	379	85-94[b]	95-99[b]	7.1-250[b]		0.07-0.16[b]	
Pleural LDH>200 U/L[2,5,66]	439	70 (64-75)	98 (93-100)	18 (6.8-46)	0	0.32 (0.27-0.38)	0
Pleural:serum cholesterol ratio >0.3[4,5,77]	496	93 (90-96)	94 (90-97)	14 (5.5-38)	67	0.08 (0.05-0.12)	0
Pleural:serum LDH ratio >0.6[2,5,6,66,77,81]	736	88 (84-91)	91 (88-94)	9.2 (5.9-14)	22	0.14 (0.10-0.20)	29
Pleural:serum protein ratio >0.5[2,5,6,66,68,77,81]	753	90 (87-93)	90 (86-93)	7.0 (2.7-18)	86	0.12 (0.09-0.16)	0
Combined, ≥1 of Light's criteria[c,2,4,5,72,75,77]	738	97 (95-98)	85 (81-89)	5.2 (3.3-8.5)	68	0.04 (0.02-0.11)	47
Pleural protein >3 g/dL[2,53,57,66]	270	88 (82-92)	86 (76-93)	5.1 (2.5-11)	37	0.14 (0.07-0.32)	67
Pleural LDH>2/3 upper limit of normal[68,77]	207	88-89[b]	93-100[b]	1.7-13[b]		0.23-0.26[b]	
Serum:pleural albumin gradient <1.2 mg/dL[72,74]	145	86-95[b]	42-100[b]	1.5-36[b]		0.06-0.32[b]	

Abbreviations: LDH, lactate dehydrogenase; OR, odds ratio.

[a] See eTables 8-10 for results from individual studies in the Supplement.

[b] For findings evaluated in only 2 studies, the range is reported rather than a point estimate with 95% CI. I^2 for heterogeneity was determined when there were at least 3 studies.

[c] Light's criteria: (1) ratio of pleural fluid protein to serum protein greater than 0.5; (2) ratio of pleural fluid LDH to serum LDH greater than 0.6; (3) pleural fluid LDH greater than two-thirds the upper limit of normal serum LDH.

reference standard for determining whether the effusion was an exudate or transudate (ie, pathology proven diagnosis). When the final diagnosis was associated with conditions expected to produce a transudate (ie, not a pathology-proven diagnosis but a clinical diagnosis such as congestive heart failure or cirrhosis), the effusion was assumed to be a transudate. Conversely, the effusion was considered to be an exudate when the final diagnosis was an infection, malignancy, or inflammatory process causing the effusion.

Exudative effusions were best diagnosed when the pleural cholesterol was greater than 55 mg/dL (n = 379; sensitivity, 85%-94%; specificity, 95%-99%; LR range, 7.1-250),[5,77] the pleural LDH greater than 200 U/L (n = 439; sensitivity, 70%; 95% CI, 64%-75%; specificity, 98%; 95% CI, 93%-100%; summary positive LR, 18; 95% CI, 6.8-46),[2,5,66] or the ratio of pleural cholesterol to serum cholesterol was greater than 0.3 (n = 496; sensitivity, 93%; 95% CI, 90%-96%; specificity, 94%; 95% CI, 90%-97%; summary positive LR, 14; 95% CI, 5.5-38)[4,5,77] (Table 1).

Adverse Events

A total of 2665 citations were retrieved regarding interventions intended to reduce the risk associated with performing a thoracentesis. Thirty-seven articles were retained after application of our inclusion and exclusion criteria (see eFigure 2, eTable 4, eTable 5 in the Supplement).[8,12,14,17,30,41,82-112] One study was rated as having high quality, 6 were of moderate quality, and 30 were of low quality, according to the GRADE criteria.[32]

The summary rate for pneumothorax following thoracentesis was 6.0% (95% CI, 4.0%-7.0%; I^2 = 95%).* The summary rate for placement of a chest tube following diagnosis of pneumothorax was slightly lower at 2.0% (95% CI, 0.99%-2.9%; I^2 = 82%).† Dry tap occurred in 7.4% of procedures (95% CI, 3.8%-13%; I^2 = 83%).‡ The risk of significant hemorrhage, defined as either hemothorax (aspiration of bright red blood through needle during procedure) or significant bleeding at puncture site after thoracentesis was 1.0% (95% CI, 0.0%-1.0%; I^2 = 49%).[17,30,86,90,100,109,111] Meta-analyses of studies reporting pneumothorax, requirement for chest tube, and hemorrhage showed possible publication bias (*P* value using the Egger regression test was .04, .02, and .02, respectively), where studies with low complication rates may have been preferentially published, but the meta-analysis of studies reporting occurrence of dry tap did not suggest publication bias (*P* value using the Egger regression test was .50). Two studies reported hypotension (range, 0.6%-1.7%)[82,97] and 2 studies reported reexpansion pulmonary edema (new or worsening hypoxemia and chest radiography consistent with edema in a reexpanded lung; range, 0.0%-16%).[82,110]

*References 8, 12, 14, 30, 41, 82-110, 112
†References 8, 41, 82-84, 86, 87, 90, 91, 93-95, 97-99, 103-107
‡References 12, 85, 91, 92, 95, 101, 105, 106, 108

Factors Affecting Performance of the Procedure

Procedural Factors

Although OR point estimates were less than 1.0 for several technical aspects of thoracentesis, suggesting fewer associated pneumothorax events, most studies reported broad CIs with an upper bound greater than 1.0 and, therefore, were not statistically significant (**Table 2**). These studies include the use of narrow-gauge compared with larger needles for both diagnostic thoracentesis (summary OR, 0.63; 95% CI, 0.10-4.0; I^2 = 76%)[83,96,102,104] and therapeutic thoracentesis (summary OR, 0.69; 95% CI, 0.13-3.7; I^2 = 67%),[85,89,104,107] and removing a smaller (500 mL–1 L of pleural fluid) rather than a larger volume (>1 L) of fluid for therapeutic procedures (summary OR, 1.3; 95% CI, 0.63-2.8; I^2 = 63%).[82,83,91,98,102]

Several needles designed specifically for thoracentesis were compared with standard needles (20-gauge; 0.91 mm diameter). For example, compared with a standard needle, the Veres needle (2.3 mm diameter)[96] had the lowest OR of all other needle types, suggesting a potential reduced risk for pneumothorax (0.14; 95% CI, 0.02-1.1). For other types of needles, the CIs were much broader: for the Boutin needle (3-mm diameter), OR 1.1 (95% CI, 0.27-4.1)[91]; for the Copes needle (3-mm diameter), OR 0.69 (95% CI, 0.19-2.5)[91]; and for angiocatheter (1.7-mm diameter), OR 0.54 (95% CI, 0.11-2.7).[12] Withdrawal of fluid through a standard needle, as opposed to a plastic catheter, may be associated with an increase in the risk of a dry tap, but the CI was broad (OR, 2.5; 95% CI, 0.51-12) and, therefore, not statistically significant.[12]

The effect of operator experience on the risk of adverse events was unclear, as the data were limited to nonrandomized trials without adequate reporting of confounders. However, no statistically sig-

Table 2. Factors Affecting Rate of Pneumothorax From Thoracentesis[a]

Factor	Patients, No.	Comparison	Summary Event Rate, %	Summary Risk Difference (95% CI)	I^2, %	Summary OR (95% CI)	I^2, %
Needle size[83,96,102,104]	1031	Smaller than 20 gauge vs larger	4.5 vs 9.3	−0.02 (−0.12 to 0.08)	91	0.63 (0.10 to 4.0)	76
Needle type[12,91,96]	34	Standard vs catheter needle (1.7 mm)[12]	20 vs 31	−0.12 (−0.41 to 0.18)		0.54 (0.11 to 2.7)	
	171	Standard vs Copes thoracentesis needle (3 mm)[91]	5.0 vs 7.0	−0.02 (−0.09 to 0.05)		0.69 (0.19 to 2.5)	
	184	Standard vs Boutin thoracentesis needle (3 mm)[91]	5.0 vs 4.8	0.00 (−0.06 to 0.06)		1.1 (0.27 to 4.1)	
	221	Standard vs Veres thoracentesis needle (2.3 mm)[96]	1.5 vs 9.2	−0.08 (−0.13 to −0.02)		0.14 (0.02 to 1.1)	
Type of procedure[85,89,104,107]	540	Diagnostic (<100 mL) vs therapeutic	4.2 vs 8.5	−0.03 (−0.14 to 0.09)	62	0.69 (0.13-3.7)	67
Volume of fluid removed[82,83,91,98,102]	2050	Smaller (range, <500mL to <1L) vs larger volume	4.1 vs 4.9	−0.01 (−0.04 to 0.02)	57	1.3 (0.63-2.8)	63
Operator experience[83,91,101,102]	1303	Less vs more experience	4.9 vs 4.6	0.01 (−0.07 to 0.02)	52	1.3 (0.53-3.0)	48
Skin marking of needle insertion site[12,99,104,106]	724	Ultrasound-guided skin marking vs localization by physical examination[b]	6.9 vs 16	−0.08 (−0.23 to 0.07)	0	0.37 (0.08-1.7)	74
Procedural ultrasound[94]	421	Ultrasound guidance at bedside during the procedure vs no ultrasound guidance[c]	0.73 vs 1.3	−0.01 (−0.03 to 0.01)		0.55 (0.06-5.3)	

Abbreviation: OR, odds ratio.

[a] See eTable 6 for results from individual studies in the Supplement.

[b] A radiologist used ultrasound to mark the skin, indicating the optimal site for needle insertion. The needle was then inserted without visualization of the pleural space.

[c] Ultrasound was used to visualize the pleural space and effusion as the needle was inserted.

nificant increase in the risk of adverse events was found when medical students or junior residents performed the procedure (ie, less-experienced operators), relative to senior residents, fellows, or attending physicians (ie, more-experienced operators) (summary OR, 1.3; 95% CI, 0.53-3.0; I^2 = 48%).[83,91,101,102]

Ultrasound Facilitation

Skin marking, performed by a radiologist using ultrasound to localize the pleural fluid and identify the optimal site for needle insertion, was not associated with a statistically significant reduction in pneumothorax (summary OR, 0.37; 95% CI, 0.08-1.7; I^2 = 74%, Table 2).[12,99,104,106] Ultrasound-guided bedside needle insertion was also not statistically associated with a decreased risk of pneumothorax (OR, 0.55; 95% CI, 0.06-5.3).[94] However, the benefit of needle insertion with ultrasound guidance may differ between patients with large vs smaller effusions or between those with loculated vs free-flowing effusions.[99] Further studies are needed because currently available data are limited.

Among patients with smaller effusions, needle insertion with ultrasound guidance at the bedside may be associated with a lower risk of a dry tap compared with use of a decubitus chest radiograph for localizing the effusion (OR, 0.23; 95% CI, 0.07-0.72), but there were no statistically significant associations among multiple needle passes (OR, 0.38; 95% CI, 0.13-1.1) or pneumothorax (OR, 0.44; 95% CI, 0.12-1.7).[99] Results were similar for patients with loculated effusions. Needle insertion with ultrasound guidance confers benefits for dry tap (OR, 0.11; 95% CI, 0.02-0.70) but not for multiple passes (OR, 0.20; 95% CI, 0.04-1.2) or pneumothorax (OR, 0.78; 95% CI, 0.06-10).[99] For patients with larger effusions, there may be no benefit of needle insertion with ultrasound guidance, although the broad CIs make this conclusion uncertain: for dry tap, OR 0.40 (95% CI, 0.04-3.9); for multiple passes, OR 1.9 (95% CI, 0.30-12); and for pneumothorax, OR 1.0 (95% CI, 0.33-3.3).[99]

Symptoms During the Procedure

Table 3 shows that respiratory symptoms (eg, dyspnea or cough) experienced during thoracentesis could cause or be caused by pneumothorax. Regardless of the chronology, such symptoms identify patients who are much more likely to experience pneumothorax (summary OR, 69; 95% CI, 3.2-1491; I^2 = 87%).[8,83,89] A similar increase in the odds of pneumothorax was observed with aspiration of air during performance of thoracentesis (summary OR, 52; 95% CI, 13-216; I^2 = 39%).[8,83,93] Despite a broad CI, the summary OR suggested that the risk of pneumothorax may increase with an increasing number of needle passes; however, it did not reach statistical significance (summary OR, 2.3; 95% CI, 0.55-9.8; I^2 = 70%).[83,91,93]

Limitations

Reviewing the characteristics distinguishing exudative from transudative effusions was difficult because many studies did not use an appropriate reference standard. The physician must make a clinical diagnosis of the cause of the effusion (eg, malignancy, congestive heart failure, or pneumonia). Therefore, studies that did not investigate beyond assessment of Light's criteria (which represent an intermediate end point rather than the underlying diagnosis), may have incorrectly categorized effusions as being transudate or exudate, particularly if it was assumed that the character of the fluid rules in or rules out a particular diagnosis.

Substantial heterogeneity was found in how thoracentesis procedures were performed. Furthermore, this study was also unable to fully explore possible differences in the likelihood of adverse outcomes from therapeutic procedures vs diagnostic ones. For example, because the effusions are larger, pneumothorax rates may be lower for therapeutic procedures than for diagnostic procedures (although patients undergoing therapeutic thoracentesis would most certainly have a greater risk of reexpansion pulmonary edema).[110] Pneumothorax rates in this analysis were lower than

Table 3. Thoracentesis-Related Factors Identifying Patients at Risk for Pneumothorax

Source	Patients, No.	Summary Event Rate, %	Summary Risk Difference (95% CI)	I^2, %	OR (95% CI) for Pneumothorax	I^2, %
Patient experienced symptoms during procedure						
Aleman,[83] 1999	506	70 (symptomatic) vs 0.20 (asymptomatic)	0.33 (0.05 to 0.61)		1 141 (129 to 10 000)	
Capizzi,[89] 1998	104	75 (symptomatic) vs 5.8 (asymptomatic)	0.69 (0.17 to 1.1)		49 (4.4 to 545)	
Collins,[8] 1987	129	42 (symptomatic) vs 8.5 (asymptomatic)	0.70 (0.50 to 0.90)		7.6 (2.1 to 29)	
Summary OR			0.57 (0.32 to 0.82)	56	69 (3.2 to 1491)	87
Air aspirated during procedure						
Aleman,[83] 1999	506	80 (air aspirated) vs 3.2 (no air aspirated)	0.77 (0.42 to 1.1)		122 (12.9 to 1157)	
Doyle,[93] 1996	174	31 (air aspirated) vs 2.5 (no air aspirated)	0.29 (0.06 to 0.52)		18 (4.1 to 75)	
Collins,[8] 1987	129	90 (air aspirated) vs 6.5 (no air aspirated)	0.83 (0.64 to 1.0)		1.25 (0.16 to 9.8)	
Summary OR			0.63 (0.23 to 1.0)	87	52 (13 to 216)	39
More vs fewer needle passes						
Doyle,[93] 1996	174	14 (more passes) vs 2.3 (fewer passes)	0.12 (0.01 to 0.22)		6.9 (1.6 to 29)	
Colt,[91] 1999	255	13 (more passes) vs 4.2 (fewer passes)	0.08 (−0.02 to 0.19)		3.3 (1.0-10)	
Aleman,[83] 1999	506	2.0 (more passes) vs 3.9 (fewer passes)	−0.02 (−0.05 to 0.01)		0.51 (0.12-2.3)	
Summary OR			0.05 (−0.07 to 0.17)	84	2.3 (0.55-9.8)	70

Abbreviation: OR, odds ratio.

expected,[18] which might be attributable to publication bias. Published studies might not reflect typical clinical practice and nonrandomized studies may generate misleading results (compared with randomized trials of interventions to optimize the safety of thoracentesis), even when intervention and control groups appear to have similar baseline characteristics.[113-116] Similarly, few studies assessed location of needle insertion.

This study did not find a statistically significant benefit of ultrasound marking to localize pleural fluid for the needle insertion site for pneumothorax rates. There also was no statistically significant benefit related to thoracentesis performed by either a radiologist (even when the remainder of the procedure is performed by the most capable physician after the site has been located) or a practitioner experienced in performing ultrasound-guided thoracentesis is at the bedside.[13] One reason a benefit might not have been observed may be the absence of randomized trials. The trials in this review included results from before-and-after observational studies, which tend to overestimate the effect of an intervention because of secular trends, even after application of standard methods to adjust for differences. Furthermore, the absence of subgroup analyses by ultrasound operators limits the generalizability of findings because it is unclear whether all patients would benefit equally (eg, regardless of the size of the effusion). Although the point estimates suggest that ultrasound guidance may be associated with a lower risk of pneumothorax, the CIs from extant studies suggest the possibility that this risk might be increased. The data do not allow determination of whether ultrasound is preferentially used for patients at greater risk for a complication or whether less experienced physicians request ultrasound more than experienced physicians do.

All included studies of ultrasound marking had radiologists or radiology residents in operant roles. As such, this review cannot firmly say that nonradiologist markings would be similarly effective simply because these studies do not exist. However, we acknowledge that many nonradiologist physicians are comfortable identifying an effusion with ultrasound guidance. What is not known is whether their comfort is justified by their own thoracentesis results, given the CIs that suggest the possibility of harm.

Chest radiography may not be required routinely[101,117] but should be done if the patient experiences symptoms (eg, dyspnea or cough) or air is aspirated during the procedure to rule out pneumothorax.[83,89,93] The risk of pneumothorax may have been underestimated because not all articles meeting inclusion criteria required chest radiography immediately after routine thoracentesis; however, this review did not find any evidence to support this practice.

How Thoracentesis Should Be Performed

The following description of the method to perform thoracentesis considers the best available evidence; textbooks were used to fill gaps not supported by trial evidence, and opinions from experts.

The procedure and its risks should be explained to the patient and informed consent obtained (**Figure**).[118]

Have the patient sit on the edge of the bed, leaning forward, with arms resting on a bedside table. If the patient is unable to sit upright, the lateral recumbent or supine position is acceptable.[117]

The needle should be inserted 1 or 2 intercostal spaces below the level of the effusion, 5 to 10 cm lateral to the spine.[117] To avoid intra-abdominal injury, the needle should not be inserted below the ninth rib.

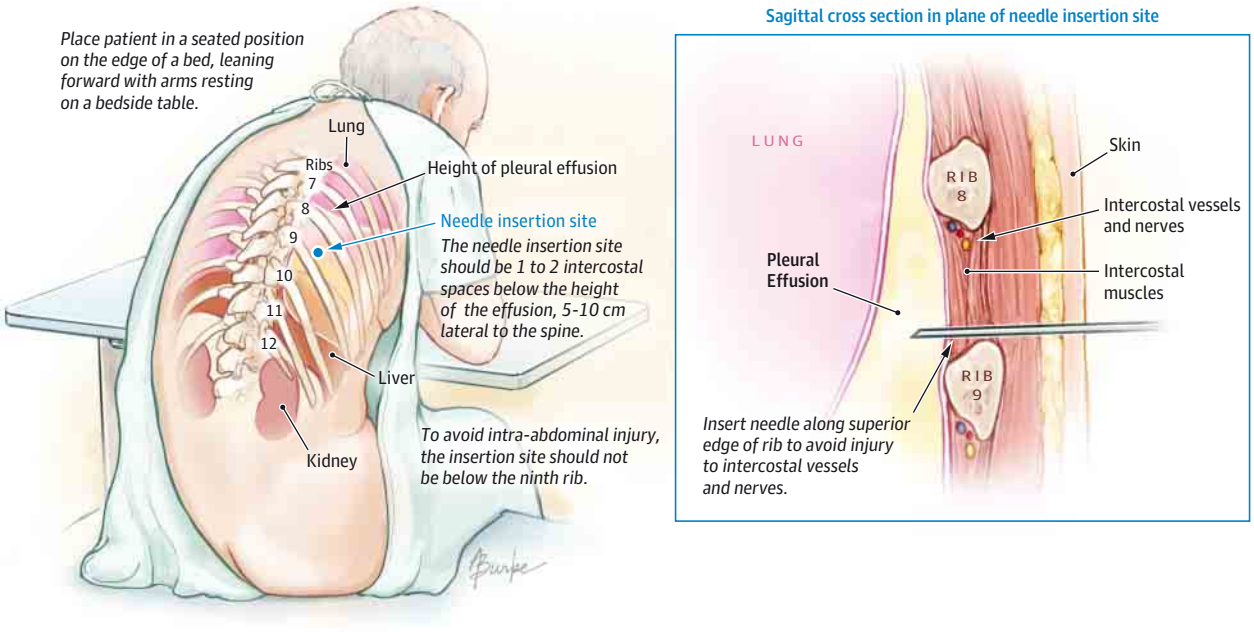
The operator should then mark the appropriate site, prepare the skin with antiseptic solution (0.05% chlorhexidine or 10% povidine-iodine solution), and apply a sterile drape.[117]

The overlying epidermis of the superior edge of the rib that lies below the selected intercostal space should be anesthetized using a small (25-gauge) needle.

A larger (20-gauge) needle should then be inserted and "walked" along the superior edge of the rib, alternately injecting anesthetic (1% or 2% lidocaine) and pulling back on the plunger every few millimeters to rule out intravascular placement and to check for proper intrapleural placement.

The needle should not touch the inferior surface of the rib so as to avoid injury to the intercostal nerves and vessels. Once pleural fluid is aspirated, additional lidocaine should be injected to anesthetize the highly sensitive parietal pleura.[117]

Figure. Patient Position and Needle Placement When Performing a Thoracentesis



Once pleural fluid is obtained, the needle should no longer be advanced, to avoid puncture of the lung. Additional lidocaine should be injected to anesthetize the highly sensitive parietal pleura.

After removal of the needle, the open hub of the catheter should be covered with a gloved finger to prevent the entry of air into the pleural cavity and a 3-way stopcock attached to the catheter hub.[117]

With the stopcock open to the patient and the syringe, aspirate a minimum of 10 mL of pleural fluid for diagnostic analysis and then close the stopcock to the patient. If additional fluid is to be removed for therapeutic purposes, one end of the high-pressure drainage tubing can be attached to the third port of the stopcock and the other end to a large evacuated container.[117] The stopcock should then be opened to the patient and the container, and the fluid should be allowed to drain. No more than 1 L of fluid should be removed during a therapeutic thoracentesis.[82,83,91,98,102]

When the procedure is complete, the needle or catheter should be removed while the patient holds his/her breath or forcibly contracts the abdominal muscles at end expiration. The site should be covered with an occlusive dressing and the remaining antiseptic solution removed from the skin.[117] All needles should be placed in appropriate safety containers.

Chest radiography is not routinely required after thoracentesis; however, it should be performed if the patient experienced symptoms such as dyspnea or cough during the procedure, or if air was aspirated.[83,89,93,117,119]

How Thoracentesis Should Be Taught or Learned

On the basis of a recent survey of internal medicine residency program directors in the United States, it was recommended that a mean of 5 thoracentesis procedures be performed (interquartile range [IQR], 3-10 procedures) to attain procedural competency and that a mean of 4 procedures (IQR, 2-5 procedures) be performed every year to maintain competency.[120] The evidence reviewed in this article indicates targets that could help clinicians assess the quality of their thoracentesis performance. Successful thoracentesis is indicated by obtaining sufficient pleural fluid for analysis on the first attempt and by achieving a rate of procedure-associated pneumothorax less than 6%.[13] However, because this figure represents the average risk of events, it cannot be considered a benchmark.[121] As such, all physicians should consider keeping personal training logs to assess their own adverse event rates.

To date, there is little evidence to guide the teaching of this procedure. Simulators[122] and procedural checklists[123,124] have been developed but have not been rigorously evaluated. One study used a pretest-posttest observational checklist to evaluate a 2-hour educational session designed to enhance procedural performance skills.[125] Using simulation technology, resident performance improved by 71% with deliberate practice.[125] More structured curricula for procedural skills training have been developed to minimize the variation in students' ability and comfort level that may arise because of random and unpredictable acquisition of basic skills through ward teaching.[126,127] The lack of data on use of bedside ultrasonography to guide needle insertion prevents us from providing guidance on how to teach this aspect of the procedure. Physicians may, however, want to consider procedural training on mannequins to determine the adequacy of their skills at thoracic ultrasound prior to clinical practice.[128] Both the American College of Emergency Physicians[129] and the American College of Surgeons[130] strongly support the use of ultrasound for thoracentesis through their policies on scope of practice, training, and maintenance of competency.[131] Further research is required to determine how best to assess clinical competency in bedside ultrasound techniques.

Scenario Resolution

The patient has heart failure (which would cause a transudative effusion), but the patient may also have pneumonia (which could cause an exudative effusion). The treating physician's clinical judgment is that there is a 50% chance of an exudative effusion. The patient's consent to perform thoracentesis should be obtained. The fluid and a sample of the patient's serum should be sent for measurement of LDH and protein; and cholesterol levels should be requested, knowing that the latter may offer better operating characteristics for distinguishing a transudative from an exudative effusion. Pleural LDH is 220 U/L (LR = 18 for an exudate), pleural protein is 54 g/L (LR = 5.1 for an exudate), pleural cholesterol is 56 mg/dL (LR range, 7.1-250), serum LDH is 342 U/L (pleural:serum LDH ratio >0.6; LR, 9.2 for an exudate), serum protein is 35g/L (pleural:serum protein ratio >0.5; LR, 7.0 for an exudate), and serum cholesterol is 156 mg/dL (pleural:serum cholesterol ratio >0.3; LR, 14 for an exudate). All of these results consistently favor an exudate and lead to initiating therapy with appropriate antibiotics and drainage of the parapneumonic effusion. Using the lowest LR for pleural protein (LR 5.1), the probability of an exudate is greater than 84%.

Clinical Bottom Line

According to a reference standard for the final clinical diagnosis, if the effusion meets none of Light's criteria, it is transudative. If the effusion meets Light's criteria or if any of the following results are obtained, the effusion is most likely exudative: pleural cholesterol greater than 55 mg/dL (LR range, 7.1-250); pleural LDH greater than 200 U/L (LR, 18; 95% CI, 6.8-46); and ratio of pleural cholesterol to serum cholesterol greater than 0.3 (LR, 14; 95% CI, 5.5-38).

No specific precaution has been definitively shown to reduce the risk of pneumothorax. However, the following may be helpful: use of a small-gauge needle (at least 20 gauge); and removal of less than 1 L of pleural fluid at a time.

Randomized trials are needed to evaluate whether ultrasound marking by a radiologist or needle insertion under ultrasound guidance at the bedside is needed for all effusions and for those of all levels of operator experience because current literature consists of primarily nonrandomized data with inherent methodological limitations.

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