Top Ten List in Pleural Disease*

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Key words: chest tube; guideline; pleura; pneumothorax; thoracoscopy

Abbreviations: ACCP = American College of Chest Physicians; BTS = British Thoracic Society; DNase = deoxyribonuclease; PFP = primary spontaneous pneumothorax

GUIDELINES

1. BTS guidelines for the management of pleural disease. Thorax 2003; 58(Suppl II)

This supplement contains six sections addressing many aspects of pleural disease. After an introductory section describing the methods to develop the guidelines and a summarization of key points, there is a section each on the investigation of a unilateral pleural effusion in adults and guidelines for the insertion of a chest drain. Management sections address pleural infection, malignant pleural effusions, and spontaneous pneumothorax. These guidelines are complementary to, and at times divergent from, earlier American College of Chest Physicians (ACCP) guidelines on spontaneous pneumothorax and parapneumonic effusions, and the American Thoracic Society statement on malignant pleural effusions. The rigor of the British Thoracic Society (BTS) grading system assessing the primary literature is potentially concerning. Grade Ia and Ib literature included meta-analyses of randomized trials and parapneumonic effusions, and the American Thoracic Society statement on malignant pleural effusions. The Bayesian approach incorporating multilevel likelihood ratios to arrive at a diagnosis differs from more traditional dichotomous testing that utilizes set cut-points. The Bayesian approach improves the accuracy of pleural fluid categorization by avoiding vague subcategories of effusions such as "pseudoexudates" arising from dichotomous testing. The authors highlighted that the Bayesian approach avoids dichotomous test results treating borderline abnormal and extreme results the same while ignoring important clinical information. Important clinical information is incorporated to determine pretest suspicion (pretest probability) for an exudative effusion. This pretest probability is then combined with the multilevel likelihood ratio for seven pleural variables (generated by Heffner and colleagues) to convert the pretest

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probability to a posttest probability of an exudative pleural effusion. Multilevel likelihood ratio tables, all applicable formulas, and an example of relevant calculations are given to ease clinicians into the use of multilevel likelihood ratios. Such formulas and data can be easily incorporated into almost any handheld device. This approach to pleural fluid analysis may eventually make obsolete the venerable Light’s criteria and be aptly recognized as the most appropriate approach to other diagnostic tests.


This randomized controlled trial evaluated the diagnostic sensitivity, specificity, negative predictive value, and positive predictive value of contrasted CT-directed pleural biopsy vs Abrams’ closed pleural biopsy in the setting of cytology negative unilateral pleural effusions suspicious for malignancy. Respective values for CT are 87%, 100%, 80%, and 100%, and for Abrams’ closed pleural biopsy are 47%, 100%, 44%, and 100% (p = 0.02, sensitivity) [subset analysis found values for CT-directed biopsy (88%, 100%, 94%, 100%) and Abrams’ biopsy (55%, 100%, 72%, 100%) in the setting of mesothelioma without statistically significant differences]. There was a 40% difference in sensitivity in favor of CT-guided biopsy. Therefore, primary use of CT-guided biopsy can avoid doing at least one Abrams’ biopsy for every 2.5 CT-guided biopsies. Parietal pleural thickening < 5 mm and ≥ 5 mm underwent biopsy by CT guidance with 75% and 100% diagnostic sensitivities, respectively. Despite the small number of patients (n = 50), the study power was 90% with 5% significance with an interim review performed at 25 patients. Currently in the United States, closed pleural biopsy has fallen into disfavor as a diagnostic tool in the setting of suspected pleural malignancy undiagnosed by initial thoracentesis, with repeat thoracentesis or thoracoscopy often favored. A underscore that the diagnostic sensitivity of CT-guided biopsy (87%) is only slightly less than the published sensitivities from two large thoracoscopy series (95%) while being less invasive, less costly, and safer. Repeat thoracentesis, one to three times, at best may increase the diagnostic yield for malignancy by 17%


Sallach and colleagues challenged the need to send a large volume of fluid to increase cytologic yield in the setting of a suspected malignant pleural effusion. This retrospective study of 374 thoracentesis samples in 282 patients divided samples into quartiles based on the fluid volume submitted. Each quartile had approximately the same number of samples with the following volumes: ≤ 10 mL, 15 to 50 mL, 100 to 755 mL, and 800 to 2,800 mL. Neither the diagnostic sensitivity nor the negative predictive value for pleural malignancy was found to depend on the volume of fluid submitted. As little as 10 mL of pleural fluid appeared adequate for diagnosing pleural malignancy. A linear relationship between pleural fluid volume submitted and diagnostic sensitivity was in a positive direction but not statistically significant. An ongoing prospective study from the same institution (personal communication; Paul Kvale, MD; April 2003) may answer whether a larger volume of pleural fluid may be more sensitive. Meantime, as little as 10 mL of fluid currently appears adequate.

Chest Tube Management


The maximum allowable daily volume of chest tube fluid output prior to tube removal remains unestablished by evidence. The prospective randomized trial of Younes and colleagues of 139 postthoracotomy patients found no difference in drainage time, hospital stay, fluid reaccumulation rates, and thoracentesis rates among patients with their chest tubes removed at a daily threshold output rate of ≤ 100 mL/d, ≤ 150 mL/d, or ≤ 200 mL/d. No sign of pleural infection or air leak could be present prior to chest tube removal. Thoracotomy procedures included exploratory thoracotomies, wedge resections, and lobectomies. This finding was subsequently validated in 91 prospectively enrolled consecutive patients. A power analysis noted that the sample size used enabled a detection of a 20 to 25% change in pleural fluid reaccumulation, with a power of 80%. The authors did not indicate if a Bonferroni correction (for the multiple comparisons using the Student t test) was performed. Regardless, this study is a valuable addition to an area with limited existing information. Similar prospective randomized studies in medical patients with recurrent benign or malignant pleural effusions undergoing pleurodesis are needed given the potential impact of chest tube time on hospital length of stay and overall procedure cost. Only one limited medical study (n = 25 patients) addressing prepleurodesis fluid chest tube output and its relation to pleurodesis success exists.

A commonly asked question is whether to remove a chest tube at end-inspiration or end-expiration. The prospective randomized study of Bell and colleagues of 102 chest tubes in 69 blunt or penetrating thoracic trauma patients (n = 52, end-inspiration; n = 50, end-expiration) found no significant difference in post-chest tube removal pneumothorax rates (end-inspiration, 8%; end-expiration, 6%). The presence of hemothorax, history of thoracotomy or thoracoscopy, previous lung disease, chest tube duration, presence of more than one chest tube in the same hemithorax, and a small (but stable) pneumothorax at time of tube removal did not affect the pneumothorax recurrence rate. Interestingly, chest tubes were removed if fluid output was < 200 mL/d, lending additional support to the findings of No. 5, above.

PNEUMOTHORAX MANAGEMENT


Manual aspiration was variably incorporated as the initial management of patients with a first-time primary spontaneous pneumothorax (PSP) in the United States in 1996. Aspiration is not embraced by the ACCP spontaneous pneumothorax Delphi consensus statement, but is favored by the current BTS pneumothorax guidelines (see No. 1, earlier). Disparity in aspiration adoption exists due to the limited data assessing the efficacy of aspiration. Only two prior randomized controlled trials assessing aspiration efficacy in PSP patients exist; both suffer significant design flaws. The recent, prospective, multicenter pilot study of Noppen and colleagues enrolled 60 patients with first-time PSP randomized to manual aspiration (n = 27, 16-gauge IV catheter) or chest tube drainage (n = 33, 16F or 20F chest tubes). This study noted no difference in immediate success, 1-week success, hospital days, 1-year pneumothorax recurrence, or urgent readmissions between the two groups. Although the study has “only a < 25% probability of not missing meaningful differences between endpoints” between the two groups, it provides preliminary data inferring possible equivalence of aspiration and chest tube placement in PSP patients. Future study is needed to assess if there is any superiority of aspiration compared with chest tube placement. However, such study may be irrelevant given the availability of commercial all-in-one chest tube kits for placement of a small-bore chest tube (8F to 16F) that may be used for initial aspiration and easily left in place if a continued air leak exists.

PleurODeSIs


Prior study of pleural sclerosing solutions has proven that patient rotation is unnecessary, as the solution likely spreads by capillary action. No such assessment of sclerosing talc suspensions (“talc sludge”) has been performed. Mager and colleagues prospectively enrolled 20 patients with malignant pleural effusions treated with talc pleurodesis (4-g suspension randomized to rotation (n = 10) or supine position (nonrotation, n = 10) for 1 h after chest tube instillation of t alc. All patients received a bone scintigram to visualize the contours of the chest cavity. The talc suspension was radiolabeled to assess intrapleural talc dispersion. Talc distribution was found to be poor, covering < 50% of the pleural cavity in 75% of all patients regardless of rotation status. Talc distribution occurred rapidly with no change after 1 h, and tended to be confined to an area around the tip of the chest tube. No differences were found between rotated and nonrotated patients regarding talc distribution or success of sclerosis after 1 month (85% overall success, and no recurrence of pleural fluid). Therefore, rotation of patients treated with intrapleural talc suspension is unnecessary. Because of the success of talc despite limited distribution, the authors speculate that distribution is not the sole determinant of talc success. Instead, locally triggered proinflammatory cytokines are postulated to drive intrapleural spread of inflammation and fibrosis. Perhaps the intrapleural inflammatory response rarely spreads systemically triggering development of acute respiratory failure? The incidence and cause(s) of talc associated acute respiratory failure continue to be debated.

PLEURAL TUBERCULOSIS


Early pleural fluid drainage has been suggested to improve outcomes in patients with tuberculous pleural effusions. Lai and colleagues prospectively ran-
domized 61 patients to treatment with antituberculous medications (isoniazid, rifampin, pyrazinamide, and ethambutol) combined with early pigtail catheter drainage \( (n = 30) \) vs treatment with antituberculous medications alone \( (n = 31) \). Outcomes were assessed over 24 weeks, with the patients’ initial effusions ranging in size from small (less than one third of one hemithorax; \( n = 2 \), each group), to moderate (between one third and two thirds of one hemithorax; \( n = 15 \), \( n = 16 \), respectively), to large (more than two thirds of one hemithorax; \( n = 13 \), each group). The only significant difference found was more rapid resolution of dyspnea in the catheter group (median, 4 days vs 8 days). However, there was no difference in the visual analog score (combined index of dyspnea, general well being, appetite, night sweating, pleural chest pain, tiredness, and cough) after 1 week of treatment. No difference was found in FVC or residual pleural thickening at the end of treatment. Early pleural drainage in the setting of tuberculous pleural effusions appears to offer no measurable advantages over routine antituberculous drug treatment alone.

**The Future?**


While the efficacy of intrapleural fibrinolytics continues to be assessed in parapneumonic effusions and empyemas, the ACCP guidelines2 and BTS guidelines (see No. 1, earlier) recommend fibrinolytics in certain pleural infection settings. The case report by Simpson and colleagues offers a glimpse into a potential alternate future management option for parapneumonic effusion and empyema. They reported a case of an 83-year-old woman with an empyema with limited response to antibiotics and sequential unsuccessful management with large-volume thoracentesis, intercostal catheter drainage, and a second intercostal catheter insertion including streptokinase infusion. The patient refused further thoracic surgical intervention and consented to intrapleural administration of human recombinant deoxyribonuclease (DNase) [dornase alfa]. After 3 days of 5 mg of intrapleural DNase daily, the patient demonstrated considerable chest radiographic and systemic symptom improvement. The authors speculated that DNase-driven depolymerization of polymerized deoxyribonucleoproteins derived from leukocytes within the empyema made the pleural fluid less viscous and easier to drain. They noted that older preparations using a combination of streptokinase and streptococcal DNase intrapleurally appeared more efficacious in empyema patients. They suggested that the DNase component produced the better outcomes. The recent international meeting of the American Thoracic Society Master Clinicians (Seattle, WA, May 2003) presentation on pleural disease noted similar success with intrapleural DNase in an empyema patient (Robert Davies, Fergus Gleesone, Nick Maskell, Oxford, UK).16 Perhaps DNase should be the future research front in the management of pleural infections?

**References**

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