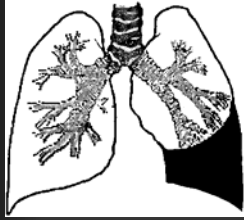


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Contact: vcgarylee@hotmail.com

Pleural Diseases in Pregnancy

Richard W Light MD

Vanderbilt University, Nashville, TN, USA
rlight98@yahoo.com

Pleural effusion: To my knowledge, there has never been a systematic study on the diseases causing pleural effusion in pregnancy. There is a high incidence of small pleural effusion demonstrable by ultrasonography in pregnant women. In one study of 47 patients, studied at a mean gestation of 24.4 weeks, 28 (59.5%) had free pleural fluid which was bilateral in 18 (38.3%) and unilateral in 10 (21.2%)¹. The mean thickness of the pleural fluid was 2.9±1.1mm. The patients with pleural fluid were asymptomatic. These same workers reported that the prevalence of demonstrable pleural fluid was 25% in 106 normal individuals.

When patients develop symptomatic pleural effusions, several different diseases should be considered. Early in pregnancy, one diagnosis that should always be considered is the ovarian hyperstimulation stimulation syndrome (OHSS)². OHSS occurs in approximately 3% of patients undergoing superovulation with gonadotropins. This syndrome is characterized by ovarian enlargement and fluid shifts, resulting in intravascular volume depletion. The severe syndrome is life-threatening and is characterized by massive ascites and/or hydrothorax and increased blood viscosity. It is thought that OHSS results when the hyperstimulated ovary produces cytokines or other vasoactive substance that enter either the systemic circulation or the peritoneal cavity to produce the syndrome via increasing capillary permeability. The cytokine that is most likely to be responsible for OHSS is vascular endothelial growth factor. The treatment of OHSS is primarily supportive.

The distribution of the other causes of pleural effusions in the pregnant individual is probably similar to those of non-pregnant women of the same age. In general, I would guess that the leading cause of pleural effusions during pregnancy is pulmonary embolism. The relative risk of venous thromboembolism among pregnant or postpartum women is 4.29 compared with non-pregnant

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women. The risk of pulmonary embolism is much higher (~15 times) in the postpartum period than during pregnancy³. Other common causes of pleural effusions include pneumonia with effusion and viral illnesses. The incidence of pleural effusions is low (~3%) in patients with severe preeclampsia or the HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome⁴. If the patient has a transudative effusion, peripartum cardiomyopathy, which complicates approximately 1 in 300 pregnancies, should be considered.

As mentioned earlier, there is a high incidence of pulmonary embolism in the postpartum period. One other entity that should be considered in the postpartum patient with pleural effusion is the anti-phospholipid syndrome². Patients with this syndrome present with a systemic illness characterized by fever, pleural effusions and pulmonary infiltrates within a few weeks of delivery. Laboratory tests reveal that the patients have either lupus anticoagulant or anticardiolipin antibodies or both, but do not have antinuclear antibodies. Treatment for this syndrome is immunosuppressive therapy after pulmonary embolus and infection have been carefully ruled out².

Pneumothorax: Spontaneous pneumothorax can occur during pregnancy, but it is uncommon. As of 2002 only 42 cases had been described⁵. About 50% of patients have a predisposing factor for pneumothorax such as an underlying infection, asthma, a history of pneumothorax or cocaine use. The treatment for spontaneous pneumothorax associated with pregnancy is the same as for spontaneous pneumothorax in the non-pregnant individual.

Pneumomediastinum and pneumothorax can be associated with labor. It occurs mainly in young primiparous women during the second state of labor. It is thought that the pneumomediastinum is due to increased intraluminal and intra-alveolar pressure occurring during the Valsalva maneuvers during labor which causes alveolar rupture. Subsequently the air dissects to the mediastinum and if the mediastinal pleura ruptures, a pneumothorax develops. Most patients require only conservative management consisting of reassurance, supplementary oxygen and analgesics.

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Pleural Infection in Children

Anne H Thomson MD FRCP FRCPC

John Radcliffe Hospital, Oxford, U.K.

anne.thomson@orh.nhs.uk

In the last decade there has been a change in the approach to pleural infection in children. Good quality ultrasonography has permitted visualization of pleural collections; small bore catheters and fibrinolytics have been introduced for medical management and the surgical approach has moved from an open to a video assisted thoracoscopic procedure (VATS). The results are impressive with an average hospital stay post intervention of approximately seven days.

The first randomized controlled trial of fibrinolytics in children was published in 2002¹. Sixty children were randomized to either urokinase or saline with the main outcome being length of hospital stay post intervention. Results were in favor of urokinase (7.4 vs 9.5 days; $p < 0.03$). Subsequent case series have confirmed that the trial results are reproducible in clinical practice² and with alteplase (tPA) as well as urokinase.

Surgeons find these results surprising and have moved to tackle pleural infection using VATS as the initial procedure. A recently completed head-to-head randomized trial of fibrinolytic therapy versus VATS, powered to show a two-day difference in hospital stay post procedure, found no difference between the two approaches. However, economic analysis shows that VATS is significantly more expensive³.

These results are in contrast to the adult experience with a controlled trial of intrapleural streptokinase (MIST) demonstrating that fibrinolytics have no effect in adult pleural disease⁴. The MIST trial was powered for differences in mortality or need for surgery. Up to 15% of adults with pleural infection die and 15-40% require surgery. In contrast, mortality in children in the developed world is less than 0.1%.

Other differences between empyemas in adults and children include:

Co-morbidity: Most adults who develop empyema have co-existing disease (65% and 72% of the groups in the MIST study)⁴. In contrast, most children are previously entirely well².

Nutrition: Serum albumin levels in the adult patients of the MIST study were low. whereas case series of children with empyema have shown normal albumin levels².

Organisms: New molecular techniques have shown that in children *Streptococcus pneumoniae* is the principal organism (86% in whom organisms were found; 66% of all cases)⁵. In the MIST study, *S. pneumoniae* accounted for 22% of patients in whom organism identified (13.6% of all cases)⁶. Hospital acquired infections are very rare in children but accounted for 10 to 12% of the adult cases.

Recovery: Children heal rapidly. Chest x-rays taken at 6-8 weeks post empyema usually show clear lung fields with residual pleural thickening of 2-3 mm (fig 1). In contrast, three months after their illness adults still have an average of 12 to 15 mm of pleural thickening⁴.

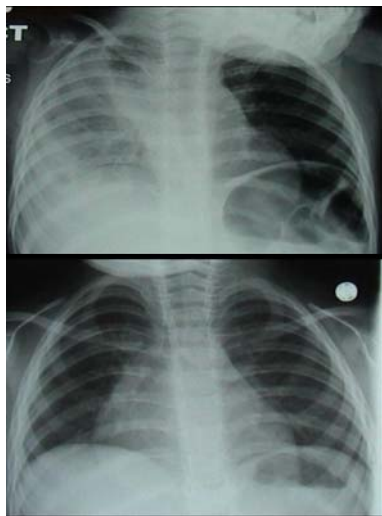


Fig 1. Chest x-rays of a child with empyema at discharge (above) and six weeks later (below), showing continual healing.

In western society, parapneumonic infection in children is different from adults. The common organisms are gram positive ones and the pleural infection is usually community acquired. Children who suffer from pleural infection are often previously healthy, well nourished, and will respond well to pleural drainage with fibrinolysis and heal rapidly. This is a good reminder that children are not small adults.

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IMAGES OF THE PLEURA

Barium in the Pleural Space

José Manuel Porcel MD FCCP
jporcel@yahoo.es

Miguel León MD

Arnau de Vilanova University Hospital, Lleida, Spain



A 73-year-old man presented with fever and dyspnea four days after a subtotal gastrectomy with Roux-en-Y reconstruction for gastric adenocarcinoma. A chest radiograph revealed a left-sided pleural effusion. A diagnostic thoracentesis demonstrated a purulent fluid with isolation of *Escherichia coli*, *Serratia marcescens* and *Candida* spp. on cultures. A thoracoabdominal CT scan showed accumulation of the barium material in the left pleural space (Figure). Upper GI endoscopy confirmed the presence of a fistulous tract in the distal esophagus. In addition to broad-spectrum antibiotics and tube thoracostomy, the patient underwent distal esophagectomy. Unfortunately, he died from acute gastrointestinal bleeding after surgical intervention.

Diagnosis: Empyema secondary to postoperative esophageopleural fistula

Milky Pleural Fluid

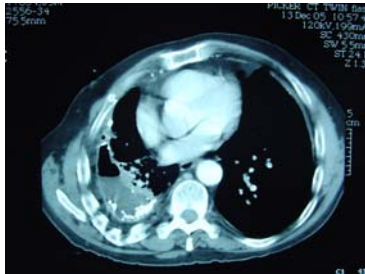
José Manuel Porcel MD FCCP
jporcelp@yahoo.es

Dolors Domingo MD
Arnau de Vilanova University Hospital, Lleida, Spain

A 69-year-old man presented with a 2-week history of fever and productive cough. He reported a remote history of artificial pneumothorax presumably used to treat tuberculosis, and had advanced chronic obstructive pulmonary disease. A chest radiograph revealed lung collapse, and a moderate right-sided pleural effusion with pleural calcification (Fig 1).



A thoracic CT scan showed rib thickening, as well as loculated pleural fluid (Fig 2).



The pleural fluid was an exudate with abundant polymorphonuclear leukocytes. The pleural fluid analysis showed an adenosine deaminase level of 243U/L, a cholesterol level of 90mg/dL, a triglyceride level of 50mg/dL, and numerous acid-fast bacilli on staining.



The pleural fluid was milky in appearance (Fig 3). After centrifugation, the supernatant was clear. In the following days, the patient produced copious amount of 'milky' sputum, suggestive of the development of a bronchopleural fistula. He is currently being treated with anti-TB drugs, along with serial thoracentesis.

Diagnosis: Tuberculous empyema

If you have any comment on the Newsletter or any interesting cases of pleural disease, contact:

Dr Y C Gary Lee
ycgarylee@hotmail.com

Pleural Disease: Clinical Year-in-Review 2005

Oner Dikensoy MD
Gaziantep University, Gaziantep, Turkey
dikensoy@yahoo.com

Several large randomized trials were published in 2005 examining different aspects of pleural diseases, the results of which may have implications on clinical practices.

U.K. Controlled trial of intrapleural Streptokinase for pleural infection: Maskell NA, et al. N Engl J Med 2005; 352:865-74

Approximately one million patients are hospitalized in the United States each year with pneumonia, of which 20 to 40% develop a parapneumonic effusion¹. Complicated parapneumonic effusions require drainage of the pleural space for the resolution of pleural sepsis and the prevention of empyema. The optimal treatment of complicated parapneumonic effusions and empyema remains controversial.

Intrapleural administration of fibrinolytic agents for complicated parapneumonic effusions has been the topic of investigation in several controlled studies, but the study by Maskell et al was the largest². In this double-blind, multicenter trial, 454 patients with pleural infection (defined by the presence of purulent pleural fluid or pleural fluid with a pH <7.2 with signs of infection or by proven bacterial invasion of the pleural space) were randomized to receive intrapleural streptokinase (250,000 IU twice daily for three days) or placebo. Patients received antibiotics and underwent chest-tube drainage, surgery, and other treatment as part of routine care. No significant differences were found between the groups in mortality or need for surgery (with streptokinase: 64 of 206 patients [31%]; with placebo: 60 of 221 [27%]; relative risk 1.14 [95% C.I. 0.85–1.54]; p=0.43). Streptokinase offers no benefits in radiographic outcomes or length of hospitalization.

The results of this study cast doubt on the effectiveness of intrapleural fibrinolytics. Although the authors concluded that fibrinolytic therapy 'should generally be avoided in pleural infection', whether fibrinolytics have a role in selected subgroups of patients continues to be debated.

Randomized phase III study of Cisplatin with or without Raltitrexed in patients with malignant pleural mesothelioma: van Meerbeeck JP, et al. J Clin Oncol 2005; 23:6881-9.

Malignant pleural mesothelioma is an aggressive tumor with poor prognosis. The prevalence of malignant pleural mesothelioma is increasing worldwide.

Recently, van Meerbeeck et al³ reported a randomized phase III trial of cisplatin with or without raltitrexed, an antifolate, in the treatment of malignant pleural mesothelioma. They randomized 250 patients (80% male; median age, 58 years) to receive cisplatin 80 mg/m² IV on day 1, alone or combined with 3 mg/m² of raltitrexed. The median survival with cisplatin alone was 8.8 (95% CI, 7.8 to 10.8) months, compared with 11.4 months (95% CI, 10.1 to 15) in the cisplatin + raltitrexed group; and the 1-year survival was 40% with cisplatin alone vs 46% with the addition of raltitrexed (p=0.048). The response rates were 13.6% (with cisplatin alone) versus 23.6% (cisplatin + raltitrexed), p= 0.056. No difference in health related quality of life (HRQOL) was observed on any of the instruments used.

This well-designed study confirms that the efficacy of cisplatin and an antifolate in patients with malignant pleural mesothelioma, without harmful effect on HRQOL. Previously, a similar phase III randomized controlled study showed a beneficial effect of combining cisplatin with another antifolate, pemetrexed, over cisplatin alone⁴. The results of these two studies taken together argue strongly that the combined chemotherapy using an antifolate (eg raltitrexed) with cisplatin should be considered in patients with mesothelioma.

Phase III intergroup study of Talc poudrage vs Talc slurry sclerosis for malignant pleural effusion: Dresler CM, et al. Chest. 2005;127:909-15

Chemical pleurodesis is the most widely used method in the management of symptomatic malignant pleural effusions. Talc is the most commonly used pleurodesing agent worldwide. The optimal route of delivery (slurry vs poudrage) of talc remains controversial.

Dresler et al reported the largest prospective randomized controlled trial for pleurodesis. This study compared thoracoscopy with talc insufflation (TTI) with talc slurry (TS) via thoracostomy for patients with malignant pleural effusions⁵. Eligible patients were randomized to TTI (n=242) or TS (n=240). No significant differences were found between the study arms in the percentage of patients with successful 30-day outcomes (TTI 78%; TS 71%). However, the subgroup of patients with primary lung or breast cancer had higher success with TTI than with TS (82% vs 67%). Respiratory complications were more common following TTI than TS (14% vs 6%). Respiratory failure was observed in 4% of TS patients and 8% of TTI patients, accounting for five and six toxic deaths, respectively.

This study found no significant advantage in thoracoscopic talc pleurodesis. In addition, it raises further concern over the safety of talc as a sclerosing agent.

Prospective randomized trial of Silver Nitrate vs Talc slurry in pleurodesis for symptomatic malignant pleural effusions: Paschoalini MS, et al. Chest 2005;128:684-9.

Currently, talc is the most widely used pleurodesing agent. However, increasing concern on its safety leads to an ongoing search for an alternative agent for pleurodesis. Silver nitrate is the first chemical used for pleurodesis. However, its use was abandoned due to severe pain that occurred after intrapleural injection of silver nitrate. Silver nitrate was brought back into practice by Professor Vargas' group in recent years. Paschoalini et al⁶ conducted a randomized controlled study to compare pleurodesis with talc and silver nitrate. Sixty patients were randomized to receive either 5 g of talc (in 50 mL), or 20 mL of 0.5% silver nitrate via the chest tube. Patients were clinically evaluated before and after treatment regarding pain, and were assessed at monthly intervals for fluid re-accumulation. Forty-nine patients returned at 30 days for follow-up (24 patients received silver nitrate; 25 received talc). Both agents appeared effective. No differences were found between the groups in the amount of fluid drained or the level of pain. No patient in either group developed ARDS. The mean numbers of hospital days were similar.

This is the first randomized controlled study to compare silver nitrate against talc as a pleurodesing agent in human. Although further studies are needed to confirm the long-term efficacy and safety of silver nitrate, this study supports silver nitrate as a reasonable alternative to talc for pleurodesis, with a similar efficacy and no significant side effects. In addition, silver nitrate is cheap and readily available.

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