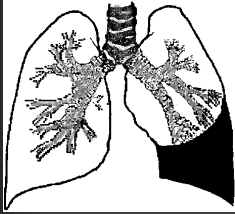


# International Pleural Newsletter



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## Parapneumonic effusions

### *Pneumococcal Empyema*

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Pneumococcal empyema is one of the most common complication of pneumococcal pneumonia as well as an important cause of morbidity and mortality worldwide. In the pre-antibiotic era, empyema involved 5% of pneumonia cases, but with the development of antibiotics the rate declined to 2%. In recent decades, the incidence of empyema has started increasing worldwide.

At the beginning of the 21<sup>st</sup> century, the heptavalent pneumococcal conjugate vaccine (PCV7), which protects against 7 of the most common pneumococcal serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F), was introduced in practice to prevent pneumococcal infections in children, a high risk population for the disease. Its widespread use has been accompanied by substantial reductions in the occurrence of the disease caused by those serotypes. But, a dynamic process of replacement seems to have occurred and the incidence of pneumococcal infections caused by non-PCV7 serotypes has increased<sup>1</sup>. Although the vaccine was beneficial in decreasing the overall incidence of pneumococcal disease in children, such an effect was not observed for pneumococcal empyema. In fact, different studies have reported a 2 to 5-fold increase in rates of empyema in children after the introduction of PCV7<sup>2,3</sup>. This change was associated with the emergence of serotypes 1 and 3, none of which were included in the PCV7. Similarly, a striking increase

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in the incidence of adult pneumococcal empyema has been reported, especially in those aged 18-50 years, from 7.6% in the pre-vaccine period to 14.9% in the post. The emergence of serotype 1 now causes more than 40% of empyemas in adults<sup>4</sup>.

The reasons for the high tendency of pneumococcal serotypes 1 and 3 to develop empyema are not well understood. As *Streptococcus pneumoniae* strains differ in their abilities to cause invasive disease, it is possible that those strains which are isolated in cases of empyema contain virulence genes that confer an increased ability to invade the pleural space.

The increase in the incidence of pneumococcal empyema, in both children and adults, cannot be easily explained as just a vaccine effect. Temporal trends in pneumococcal serotype distribution were described worldwide, with epidemic increases of the frequency of serotype 1, before the implementation of PCV7<sup>5,6</sup>.

In the future, information provided by the use of the 13-valent pneumococcal conjugated vaccine, which contains serotypes 1 and 3, may help us to better understand the exact role that PCV7 has played in the epidemiology of pneumococcal empyema, and could be an important step in the prevention of this complication.

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## ***Chest Radiographs in Detecting Parapneumonic Effusions***

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Bacterial pneumonia affects up to 4 million Americans annually in the community, with an additional 195,000 - 390,000 nosocomial infections<sup>1</sup>. One of the most frequent complications encountered amongst these patients is parapneumonic effusions (PPEs). Of the one million patients hospitalized with

community-acquired pneumonia (CAP) each year, 44%-57% have an associated PPE<sup>2</sup>. Up to 10% of all patients with PPEs require operative intervention so it is important to quickly recognize this complication and treat it appropriately<sup>3</sup>. Physicians frequently rely on portable anteroposterior (AP) chest x-rays (CXR), which can be of poor quality, to identify pneumonia and PPEs. It is unknown what percentage of significant effusions (those greater than 10 mm) is missed in patients having CAP by CXR alone.

A recent retrospective study performed at a single, large academic center evaluated the accuracy of CXRs in identifying PPEs<sup>4</sup>. Specifically, the authors studied lateral, postero-anterior (PA), and AP CXRs in patients with clinical and radiographic evidence of pneumonia that had had a chest CT (within 24 hours of their CXR) confirming the presence of a pleural effusion thought to be parapneumonic in nature. Interestingly, they found that all three views were equally poor in that they all missed more than 10% of PPEs. The sensitivity of lateral, PA, and AP CXRs was 85.7%, 82.1%, and 78.4%, respectively (p = 0.749); the specificity was 87.5%, 81.3%, and 76.4% (p = 0.198). As would be expected, the smaller effusions were missed more often than the larger in all three views. However, the three views combined missed 13% of effusions whose sizes were significant enough to warrant diagnostic thoracentesis. Individually, AP CXRs missed 12% of effusions > 10 mm, PA CXRs missed 16%, and lateral CXRs missed 12%.

One would have expected lateral CXRs to be more sensitive than PA and AP in detecting PPEs. The majority of effusions missed in each view were on films with lower lobe parenchymal consolidation adjacent to the hemidiaphragm, on the same side as the effusion. These results suggest that in the setting of pneumonia, the usual advantages of lateral and PA films in detecting pleural effusions<sup>5,6</sup> are lost if there is obscuration of the costophrenic angle from pulmonary consolidation. Since lower lobe pneumonia was present in the majority of CXRs that missed effusions in this study, it may be beneficial to obtain a thoracic ultrasound or chest CT in those patients. Thoracic ultrasound is increasingly being utilized to evaluate effusions given its bedside capability, lack of ionizing radiation, immediate return of information, superior sensitivity and specificity in identifying pleural effusions, and ability

to obtain secondary information (presence of loculations, volume of fluid, etc). Further study needs to be devoted to determine if all patients with acute pneumonia should have an ultrasound. At present, the results of the referenced study suggest that, at the minimum, patients with lower lobe consolidation should be strongly considered for ultrasound evaluation of PPE.

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## ***Chest CT Indicating the Need for Thoracentesis in Parapneumonic Effusions***

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Parapneumonic effusions (PPE) occur in 44% of patients with community acquired pneumonia (CAP) and have a significant risk of progression to empyema<sup>1</sup>. Given that risk, it is critical to ascertain which effusions require further intervention. While there have been numerous attempts to evaluate effusions using noninvasive techniques, including chest CT and MRI, they are unable to differentiate between exudative effusions that require intervention and those that are benign. As a result, thoracentesis remains the gold standard method of evaluation as per the ATS Guidelines<sup>2</sup>.

Classically, the decision to pursue thoracentesis is made when a lateral decubitus radiography (LDR) shows an effusion greater than 1 cm, or a lateral erect radiography (LER) measurement is  $>5$  cm<sup>1,3,4</sup>. In recent years, usage of chest CT has grown in popularity and at our institution 40% of hospitalized CAP patients undergo it during the first 24 hours of admission. A retrospective study investigated the

measurements of PPE by CT, from the parietal pleura-fluid junction to the visceral pleura-fluid junction in the middle third of the lung (1.5 cm above



to 7.5 cm below the carina) along the mid-scapular line, where the fluid appeared thickest (*Figure*). Using linear regression, we found that the CT measurement of 2.5 cm correlated with the established calculations of LDR (1 cm) and LER (5 cm)<sup>5</sup>. Its safety was established by retrospectively evaluating the outcomes of all patients with PPE having a thickness of  $<2.5$  cm on CT. There was only 1 negative outcome potentially attributable to PPE which measured  $<2.5$  cm. Interestingly this case also had a LDR measurement of  $<1$  cm. By both measurements this patient was very close to the established values.

While it is generally believed that CT should supplant established imaging in the evaluation of PPE, we feel that in cases in which CT has already been performed it may expedite patient care to proceed with thoracentesis if the measurements are  $>2.5$  cm. In those whose values are between 2.45 and 2.50 cm clinical judgment and additional imaging may be warranted.

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## ***Intrapleural Fibrinolytics and DNase in Pleural Infection***

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Pleural infection is an increasingly common clinical problem, associated with a poor outcome<sup>1</sup>. In addition to antibiotics and tube thoracostomy, intrapleural agents have been assessed for their ability to improve drainage. Fibrinolytics are used based on the assumption that drainage is prevented in patients with pleural infection by septations within the pleural space. However, a meta-analysis of 5 studies, including MIST1, demonstrated no benefits of intrapleural fibrinolytics versus placebo<sup>2</sup>. There are several potential explanations for this: newer and more direct fibrinolytics (such as tissue plasminogen activator –tPA-) may be more efficacious in the pleural space, or fibrinolysis alone may be insufficient. Experimental data suggests pus viscosity is not reduced by fibrinolytics, but requires the addition of DNase<sup>3</sup>. This agent combination may aid in the resolution of infection if bacteria resist normal treatment by forming a surface of coiled DNA and fibrin, known as biofilm. While there is no direct evidence of biofilm formation in pleural infection, late clinical relapse and the requirement for prolonged antibiotics are consistent with this hypothesis.

Therefore, the MIST2 study assessed tPA, DNase and both together in a randomised, double blind placebo controlled study of 210 patients with pleural infection<sup>4</sup>. Patients were assigned to one of four treatment groups: double placebo, tPA + DNase placebo, tPA placebo + DNase, and tPA + DNase, used intrapleurally for a total of 3 days. The primary outcome was the amount of pleural shadowing improvement on chest radiograph using a digital assessment strategy at 7 days post randomisation. The combination of tPA + DNase resulted in significant radiological improvement compared to placebo, or either tPA or DNase alone, and was not associated with differences in adverse events, including intrapleural bleeding. Either fibrinolytic agent alone was not significantly different from the placebo.

Although the chest radiograph is the most commonly used clinical surrogate in the treatment of pleural infections, used in isolation it is only suggestive, but not demonstrative of clinical improvement. Important secondary outcome assessments were consistent with the primary result, in that combined tPA-DNase therapy reduced referrals for surgery (odds ratio = 0.17) and hospital stays (-6.7 days).

Does this study mean that intrapleural tPA and DNase should be used in all patients with pleural infection? Arguing on the side of caution, MIST2 shows that combination therapy improves the chest X-ray, while DNase or tPA alone have no effect. Also, it may improve sepsis, reduce hospital stay, and decrease likelihood of fever. However, these secondary outcomes do not provide definitive proof. MIST2 provides further evidence that fibrinolytics in isolation should not be used, and furnishes strong evidence that DNase by itself worsens outcomes and should also be avoided as a lone treatment. Use of combination therapy as 1<sup>st</sup> line treatment for pleural infection requires further randomised studies.

There are specific situations in which it may be reasonable to use the MIST2 regimen, and these include respiratory embarrassment (e.g ventilated patients with large collections) due to an infected effusion, and those patients who have failed “medical” therapy, and for whom thoracic surgery is not considered an option. However, for those in which surgery is feasible, this remains the definitive treatment of choice until proven otherwise.

Overall, it is likely that the MIST2 study represents a significant step forward in the treatment of pleural infection – perhaps not so much in terms of immediate, recommended treatment, but in our understanding of this complex disease and the direction in which further research should proceed.

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## CASE REPORT

### *Pleural Effusion Following Transarterial Chemoembolization for Hepatocellular Carcinoma*

José M Porcel MD FCCP FACP

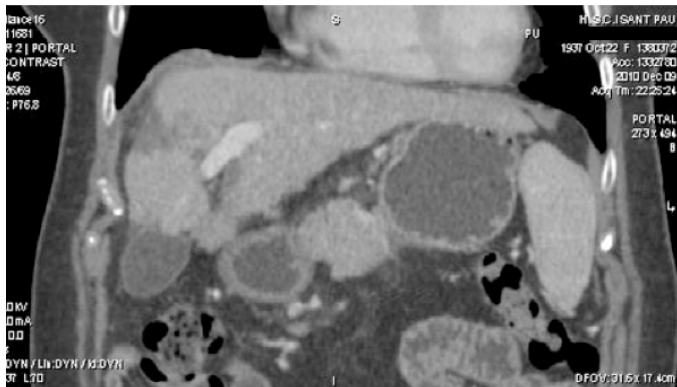
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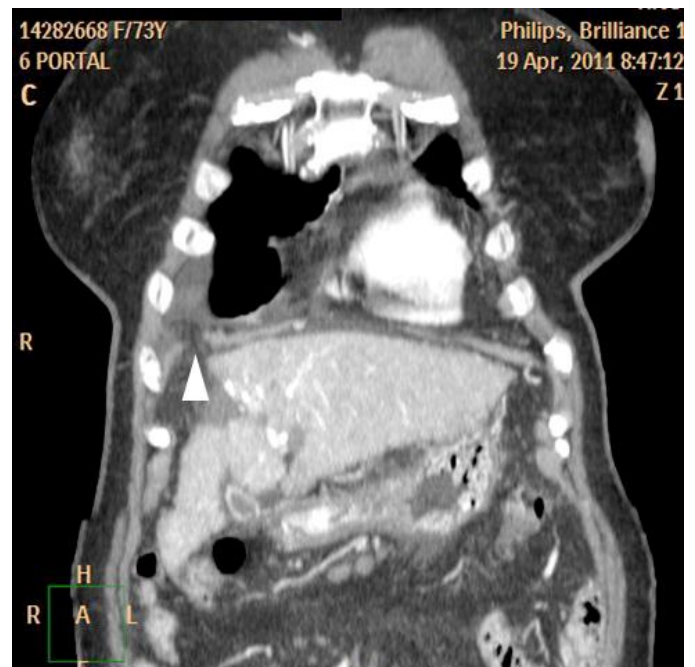
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A 73-year-old woman with hepatitis C virus infection and cirrhosis was evaluated for a 1-week history of gradually increasing dyspnea, cough and right shoulder pain. One month previously she had undergone transarterial chemoembolization (TACE) for a hepatocellular carcinoma. The technique was performed through the selective catheterization of the celiac trunk and segment IV hepatic artery with the subsequent delivery of gelatin-sponge particles and a mixture of lipiodol and adriamycin. CT scan showed diaphragm integrity (*Below*), with no evidence of pleural effusion either at that time or on a radiograph

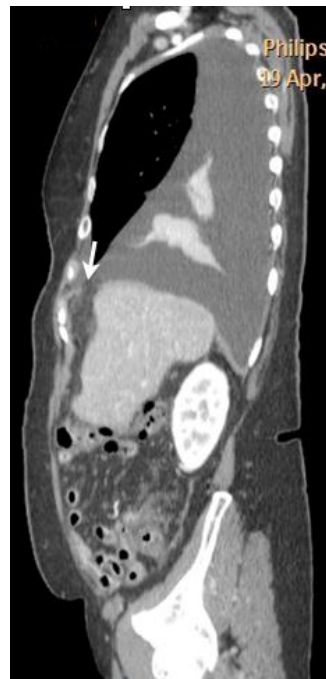


taken one week after TACE. Her liver cancer was diagnosed two years earlier, and was refractory to percutaneous ethanol ablation and radiofrequency ablation. She had also developed moderate ascites without any associated pleural effusion three years before.

On admission, the chest radiograph revealed a large right-sided pleural effusion. Pleural fluid analysis demonstrated a transudate consistent with hepatic hydrothorax. A CT scan of the chest



identified a 1.5 cm diaphragmatic hole in close contact with the hepatocellular carcinoma which had previously been chemoembolized (*Above, white arrowhead; Below, arrow*); there were no floating lipiodol aggregates in the pleural space. The patient underwent a therapeutic thoracentesis of 500 mL and received diuretics. A chest radiograph 3 months later was normal.



We hypothesized that the ischemic liver necrosis had extended to the adjacent diaphragm, generating a diaphragmatic opening which facilitated movement of the ascitic fluid from the peritoneal cavity into the pleural space. Only one similar case was found in literature<sup>1</sup>.

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