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Effect of Opioids vs NSAIDs and Larger vs Smaller Chest Tube Size on Pain Control and Pleurodesis Efficacy Among Patients With MPE: The TIME1 RCT.

Authors: Rahman NM *et al.*

Reference: JAMA 2015 Dec 22-29;314(24):2641-53.

URL: <http://jamanetwork.com.qelibresources.health.wa.gov.au/journals/jama/fullarticle/2478201>

Comment: NSAIDs are commonly avoided post-talc pleurodesis due to perceived risk of suppressing inflammation and reducing efficacy. Small-bore chest tubes are often recommended to reduce pain vs large-bore tubes, but equivalent efficacy in pleurodesis hasn't been proven. This pragmatic, 2x2 factorial randomized control trial aimed to compare the effect of tube size and analgesic choice on pain-control (superiority comparison) and pleurodesis efficacy at 3 months (non-inferiority comparison). 320 patients undergoing thoracoscopic talc poudrage (n=206) or talc slurry pleurodesis (n=114) were randomized to NSAID or opioid analgesia post-pleurodesis. The non-thoracoscopic subgroup (n=114) were also randomized to small- or large-bore chest tube.

Pain scores did not differ significantly between NSAID and opioid groups, but the NSAID group required more rescue medication (38.1% vs 26.3%, p=0.003). Pleurodesis efficacy at 3 months was not reduced in the NSAID group. Thus NSAIDs can be used as an alternative to opioids providing rescue medication is available if required.

Small-bore chest tubes were associated with a statistically significant but clinically modest reduction in pain scores while the chest tube was in situ. There were no difference in pain scores at 1 month or 3 months. There was small reduction in pleurodesis efficacy with smaller vs larger tubes (re-intervention rates of 30% vs 24% respectively).

Randomized Trial of Pleural Fluid Drainage Frequency in Patients with Malignant Pleural Effusions – The ASAP Trial.

Authors: Wahidi MM *et al.*

Reference: Am J Respir Crit Care Med. 2016 Nov

URL: <http://www.atsjournals.org/doi/full/10.1164/rccm.201607-1404OC>

Comment: The optimal drainage regimen via indwelling pleural catheters (IPC) has yet to be determined. The ASAP trial randomized patients to an aggressive daily drainage arm (n=73) or an alternate daily (standard) drainage arm (n=76). The primary endpoint was the percentage of alive patients with autopleurodesis at 12 weeks. Autopleurodesis was defined as either complete response (no residual fluid) or partial response (residual fluid not requiring intervention).

The aggressive drainage arm achieved a higher rate of patients who were both alive and had autopleurodesis than the alternate-daily arm (47% vs 24% respectively, $p=0.03$) with a shorter median time to pleurodesis. The results add support to the hypothesis that daily drainage promotes pleurodesis. However, mortality was disproportionately higher in the alternate-daily drainage arm (34% vs 25%) despite the use of validated prognostic scores, making the results difficult to interpret. Further studies are still needed to define the optimal drainage regime for IPC patients. Effects on quality of life and healthcare resources are also required to guide best practice.

Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomized, controlled, open-label, phase 3 trial.

Authors: Zalcmán G *et al.*

Reference: Lancet 2016 Apr 2;387(10026):1405-14

URL: <https://www.ncbi.nlm.nih.gov/pubmed/26719230>

Comment: Cisplatin plus pemetrexed is current first-line systemic treatment for malignant pleural mesothelioma (MPM). This open-label French study assessed the effect on overall survival of adding bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, to first-line duplet therapy in 448 patients with advanced MPM. Patients were randomized in 1:1 to the 2 treatment groups.

Addition of bevacizumab significantly increased overall survival (18.8 months vs 16.1 months in cisplatin plus pemetrexed group, $p=0.0167$) and progression free survival (9.2 months vs 7.3 months). Overall adverse event frequency was similar, but specific bevacizumab-related adverse effects (e.g. hypertension, arterial and venous thromboembolic events) were recorded higher in the cisplatin-pemetrexed-bevacizumab group.

This study supports that triple therapy with bevacizumab, cisplatin and pemetrexed should be considered as standard treatment for MPM.

The effect of chemotherapy on health-related quality of life in mesothelioma: results from the SWAMP trial.

Authors: Arnold DT *et al.*

Reference: Br J Cancer 2015 Mar 31; 112(7): 1183–1189

URL: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4385962/>

Comment: Limited data exist regarding impact of chemotherapy on health-related quality of life

(HRQoL) in patients with malignant pleural mesothelioma (MPM). The South West Area Mesothelioma and Pemetrexed (SWAMP) trial evaluated predictors of MPM response to first-line chemotherapy. This sub-study prospectively (but without randomization) evaluated health-related quality-of-life (HRQoL) outcomes. Patients were assessed at 5 time points from baseline to 18 months with HRQoL questionnaires (EQ-5D, EORTC QLQ-C30 and EORTC LC13). Of the 73 patients recruited, 58 received chemotherapy. Compliance fell from 98% at baseline to 58% at 12 months and statistical analysis was limited to Visit 3. In the chemotherapy group, the overall HRQoL (using EQ-5D) remained stable, but was significantly reduced in the non-treatment group with worse dyspnea and pain scores. Patients with non-epithelioid histology experienced a significant decline in EQ-5D compared to those with epithelioid histology. Patients who had evidence of response to chemotherapy based on CT scan at 8 weeks, or with an early fall in mesothelin level, also had better HRQoL at later time points.

As this study was not randomized, potential selection bias cannot be excluded. Nonetheless the data provides reassurance that those selected for chemotherapy at least did not compromise on quality of life.

Malignant pleural fluid from mesothelioma has potent biological activities.

Authors: Cheah HM et al.

Reference: *Respirology* 2017 Jan;22(1):192-199.

URL: <http://onlinelibrary.wiley.com/doi/10.1111/resp.12874/full>

Comment: Malignant pleural effusion (MPE) is generally considered to be a by-product of malignant disease but has previously been shown to contain numerous growth factors and cytokines suggesting potential biological activity. Cheah et al investigated this potential using human pleural fluid (56 mesothelioma, 60 metastatic carcinoma, 35 benign) in vitro, using mesothelioma cell lines, and using a mouse mesothelioma model.

Mesothelioma pleural fluid stimulated mesothelioma cell proliferation (2.23-fold) and migration (2.13-fold) in vitro. Exposing mesothelioma tumours on to MPE resulted in significantly faster growth rates compared to saline controls in a validated mouse model. Mesothelioma pleural fluid protected mesothelioma cells from chemotherapy-induced apoptosis in vitro.

The growth-stimulating effect of the fluid was not patient-specific. In a cross-over experiment, the proliferative effect of the malignant fluid samples were consistent in magnitude when the fluid was applied to mesothelioma cells from the same patient or from other patients.

This proof-of-concept study has shown pleural fluid to be a milieu that enhances tumour progression and protects it from chemotherapeutic agents.

Tissue Plasminogen Activator Potently Stimulates Pleural Effusion via a Monocyte Chemotactic Protein-1-Dependent Mechanism.

Authors: Lansley *et al.*

Reference: Am J Respir Cell Mol Biol 2015 Jul;53(1):105-12.

URL: <http://www.atsjournals.org/doi/full/10.1165/rcmb.2014-00170C>

Comment: Monocyte chemotactic protein-1 (MCP-1) induces inflammation and vascular hyperpermeability and has been implicated in the formation of exudative pleural effusions. Administration of intra-pleural fibrinolytics has been shown to significantly increase volume of effusion drained but the mechanism for this has not been previously investigated.

Using a mouse model, Lansley *et al* showed that intra-pleural administration of fibrinolytics (tPA, streptokinase and urokinase) potently induced pleural fluid production. MCP-1 levels were significantly elevated in pleural fluid vs corresponding sera and correlated with fluid volume. In vitro, using human mesothelial cell lines treated with tPA, the authors demonstrated upregulation of MCP-1 gene expression and mesothelial MCP-1 release. Antagonising MCP-1 reduced the volume of fluid by approximately 85% using either an MCP-1 antibody or an MCP-1 receptor antagonist.

These findings support and further extend the importance of MCP-1 in exudative pleural fluid formation and provide a platform to investigate its role as a therapeutic target.

Pleural Effusions at First ED Encounter Predict Worse Clinical Outcomes in Patients with Pneumonia.

Author: Dean *et al.*

Reference: Chest 2016 Jun; 149(6):1509-1515.

URL: <http://www.sciencedirect.com/science/article/pii/S0012369216004499>

Comment: Community acquired pneumonia remains a leading cause of death worldwide. The CURB-65 score and its electronic counterpart, eCURB, have been developed to predict mortality but don't take pleural effusion into consideration. Dean *et al* reviewed 4,771 patients diagnosed with CAP at first presentation to the emergency department. Those with pleural effusion at first presentation (n=690, 14.5%) had a longer length of hospital stay, higher admission rate and increased likelihood of re-presentation if discharged. This subgroup were 2.4 times more likely to die than those without pleural effusion, despite controlling for pneumonia severity and comorbidities. Though eCURB accurately predicted mortality for patients without a pleural effusion (4.7% predicted vs 5% actual), for patients with a pleural effusion mortality was significantly underestimated (7% predicted vs 14% actual).

Non-Malignant Pleural Effusions (NMPE): a prospective study of 356 consecutive unselected patients.

Authors: Walker SP *et al.*

Reference: CHEST 2017 (Epub ahead of print).

URL: <http://www.sciencedirect.com/science/article/pii/S0012369216626922>

Comment: Malignant pleural effusion is well-known to have a poor prognosis, however, little is known about outcomes of effusions secondary to benign disease. Walker *et al* prospectively followed 782 patients presenting with new undiagnosed pleural effusion and performed further analysis on the 356 (46%) of those determined to be non-malignant pleural effusions (NMPE). Diagnosis was determined at independent review by two physicians ($\kappa = 0.94$). The most common aetiology for NMPE in this cohort was infection (40.6%) followed by heart failure (24.2%). Bilateral effusions (HR 3.55 CI 2.22-5.68) and transudative effusions (HR 2.78 CI 1.81-4.28) were associated with a worse prognosis, with a 57% and 43% 1-year mortality respectively. NMPE due to cardiac, liver and renal failure had highest mortality rates (50%, 46% and 25% respectively). Interestingly, the pleural infection group had a significant one-year mortality of 19%, despite including simple parapneumonic effusions and TB pleuritis in the definition. This result is in keeping with the study by Dean *et al* (see above) and suggests that effusion associated with pneumonia is an important predictor of outcome.

Overall, this study indicates that non-malignant pleural effusions should not be considered harmless but rather a marker of disease severity and poorer prognosis.

Management of Benign Pleural Effusions Using Indwelling Pleural Catheters. A Systematic Review and Meta-analysis.

Authors: Patil *et al.*

Reference: CHEST 2017; 151(3):626-635

URL: <http://www.sciencedirect.com/science/article/pii/S0012369216623462>

Comment: There is a limited but growing body of evidence for the use of indwelling pleural catheters (IPCs) in the management of benign pleural effusions (BPE). Due to the lack of randomized controlled trials (RCTs), studies reviewed in this meta-analysis included cases series, retrospective cohort studies, and abstracts. Articles needed to have reported follow-up and outcomes. 13 studies, totaling 350 IPC placements in 325 patients were included in the final analysis. The most common causes of BPE were cardiac (49.8%), hepatic disease (12.3%), inflammatory pleurisy (6.5%), renal disease (4.0%) and chylo-

thorax (3.4%). IPCs were used for symptom control in refractory disease, as a bridge to transplant and for palliative purposes.

The primary outcome of spontaneous pleurodesis with resolution of the effusion, removal of the IPC and no need for further intervention occurred in 51.3% (160/325). There was a trend towards a lower rate of 42.1% in cardiac causes vs 61.4% in non-cardiac. Complications occurred in 17.4% of patients, similar to the rate reported for malignant pleural effusions. Patients reported overall symptom improvement. However, the quality of evidence was generally poor due to a lack of RCTs.

With the current available evidence, IPCs are acceptable interventions for patients on maximal medical management for benign pleural effusions.

ERS task force statement: diagnosis and treatment of primary spontaneous pneumothorax.

Authors: Tschopp JM et al.

Reference: Eur Respir J 2015 Aug;46(2):321-35

URL: <https://www.ncbi.nlm.nih.gov/pubmed/26113675>

Comment: This statement is a comprehensive review of available scientific evidence on primary spontaneous pneumothorax (PSP) performed by the European Respiratory Society's Scientific Committee.

The most important risk factor for PSP is tobacco smoking, with a strong dose-response relationship. Smoking cessation is the only reversible risk factor known to reduce recurrence. Other risk factors include cannabis-smoking, height and low BMI. Pathogenesis is not clear, though blebs/bullae, visceral pleura emphysema-like changes and diffuse pleural porosity may play a role. PSP reportedly recurs in 17 to 54% patients within one year.

Chest radiograph remains the standard imaging technique, but CT is more sensitive and lung ultrasonography has very high positive and negative predictive values in trauma patients.

PSP treatment is symptom-driven. Symptomatic patients at first presentation can be treated with simple aspiration, but Heimlich valves are an alternative ambulatory option. In those requiring drainage, small-bore catheters are at least as effective as large-bore (>20Fr) catheters. There is no role for immediate application of suction. Definitive treatment with thoroscopic poudrage/pleurectomy may be offered to high-risk patients or those with persistent air leak.

Novel imaging detailing the origins of a pneumothorax.

Authors: Nakanishi K *et al.*

Reference: Thorax 2017 Mar 30 (Epub ahead of print)

URL: <https://www.ncbi.nlm.nih.gov/pubmed/28360222>

Comment: Currently there is no imaging method to detect the location of the air leak in patients with pneumothorax. This prospective study of 10 patients with spontaneous pneumothorax aimed to assess ability of 3-D cine CT to visualize and identify the air leak location and bulla responsible.

These patients had air leak present 24 hours after chest drain placement. Study protocol included injection of 0.9% saline into the affected pleural cavity via preplaced chest drain, followed by a dynamic scan with a 320-multidetector row CT while patient breathed deeply.

Eight patients demonstrated dynamic motion of air during study in synchronization with breathing, allowing precise location of the leak point, which were all subsequently confirmed during surgery. No adverse effects were observed.

The authors concluded that this novel “4-D CT thoracography” can be useful for patients who require location of air leak prior to further invasive therapy such as thoracoscopic surgery or bronchial occlusion therapy.

A Novel Device for Accurate Chest Tube Insertion: A Randomized Controlled Trial.

Authors: Katballe *et al.*

Reference: Ann Thorac Surg 2016;101:527–32

URL: <http://www.sciencedirect.com/science/article/pii/S000349751501214X>

Comment: The first author of this paper developed a novel device labelled the “KatGuide” aiming to improve chest tube placement.

This multi-center randomized trial enrolled 109 patients requiring large-bore (28F) chest tube. The primary endpoint was optimal position of the tube, apical for pneumothorax and basal for pleural effusion. The KatGuide device replaces forceps during insertion and facilitates direction apically or basally. A single experienced radiologist, blinded to the method of insertion, rated tube placement as optimal or sub-optimal using CXR and CT scans.

The KatGuide method was significantly superior to the conventional method (41/49 [84%] vs 32/60 [53%] optimal tube placement, $p = 0.001$). More patients in the conventional group had misplaced tubes (11[18%] vs 2[4%]). The improved placement applied to both experienced and inexperienced operators.

This results support further evaluation of this device.



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