

TITLE PAGE

AJRCCM Submission - Beyond the Blue: What Fellows Are Reading in Other Journals

Title:

Pleural disease: saline irrigation in pleural infection, epidemiology of pneumothorax, and bevacizumab for mesothelioma.

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MAIN TEXT

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Pleural disease: saline irrigation in pleural infection, epidemiology of pneumothorax, and bevacizumab for mesothelioma.

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Recommended reading from the University of Oxford Respiratory Trials Unit and Oxford Pleural Unit clinical research fellows; Najib M Rahman DPhil, Unit and Program Director

Hooper CE, *et al.* Pleural irrigation trial (PIT): a randomised controlled trial of pleural irrigation with normal saline versus standard care in patients with pleural infection. *Eur Respir J* (1)

Reviewed by John P Corcoran

The incidence of pleural infection has increased over the past two decades, with a variety of reasons proposed for this changing clinical picture [2]. What has not changed is the morbidity and mortality associated with this condition in adults. Data from large randomised trials and case series report a one-year mortality of around 20% and an average length of hospital stay of more than two weeks. Up to one-third of patients will fail medical therapy (broad-spectrum antibiotics and tube thoracostomy) and require surgical intervention to control their infection [3-5].

There is ongoing interest in identifying means by which clinical outcomes can be improved for patients with pleural infection. Much of this work has focused on improving the efficacy of tube thoracostomy and clearance of infected material from the pleural space, especially considering that drainage becomes increasingly difficult over time as septations and loculation develop [2]. Combination intrapleural therapy with tissue plasminogen activator and deoxyribonuclease may have a positive influence on relevant clinical outcomes [5,6], but is expensive and requires further validation in large-scale clinical trials before routine use in all patients. Large-volume intrapleural saline irrigation represents an alternative and cheap approach, with case series demonstrating potential benefit. This technique is used in a number of European centres, albeit in the absence of randomised data or standardised guidance.

Hooper and colleagues [1] carried out a pilot study, recruiting 35 patients with pleural infection confirmed on the basis of widely-accepted diagnostic criteria and a residual collection after initial tube thoracostomy. Patients were then randomised to either standard chest drain care (30mL saline flushes three times daily to maintain tube patency) or pleural irrigation (250mL saline via gravity administration through the chest tube three times daily) over a three-day period. Patients were stratified according to the hemithorax volume of the pleural collection (greater or less than 25% on baseline CT evaluation) and presence of loculation on ultrasound. Clinical care was otherwise identical between groups with clinical decisions taken by a physician independent of the study team.

The study's primary outcome was percentage change in pleural fluid volume on CT thorax from the time of randomisation (day 0) to the end of the study intervention (day 3), as determined by two independent thoracic radiologists blinded to treatment arm. Patients receiving saline irrigation had a significantly greater reduction in the volume of their pleural collection on CT at day 3 compared with those receiving standard care (32.3%, IQR 19.6-43.7% vs. 15.3%, IQR -5.5-28%; $p < 0.04$). Of the secondary outcomes, the irrigation

patients were less likely to require surgical intervention for pleural infection (OR 7.1, 95% CI 1.23-41.0; $p=0.03$), but there was no significant difference in any other parameter (all-cause mortality; length of hospital stay; fall in white cell count, C-reactive protein or procalcitonin; total volume of fluid drained; frequency of adverse events) assessed. Saline irrigation was well tolerated with no serious side-effects reported.

This study shows that intrapleural saline irrigation, an easily accessible and cheap intervention, is safe and associated with a reduction in the size of residual collection and the subsequent need for surgical referral in patients with pleural infection when compared to standard care. This therapy would be appropriate for all patients acutely diagnosed with pleural infection (i.e. clinical evidence of infection in association with pleural fluid pH <7.2 and/or glucose <3mmol/L; Gram stain or culture positive fluid; and/or macroscopically purulent fluid) in whom initial tube thoracostomy has failed to achieve adequate clearance of the pleural collection after 24-48 hours. There are limitations to the study, notably the small number of patients and lack of blinding within both the study and clinical teams overseeing patient care. However, while no power calculations were done for this pilot study, it appeared to be adequately powered (a priori) for the primary outcome measure. The decision to refer for surgery may also have been influenced by the findings of the day 3 CT which were available to the responsible ward physician. However, the 3-month follow-up data (lung function and chest X-ray opacification) were similar across both treatment arms, implying the reduced surgical rate in the irrigation group had no impact on long-term respiratory outcomes.

Saline irrigation may improve clinical outcomes in pleural infection through dilution and washout of infected material and inflammatory mediators; alongside the mechanical effect of disrupting formation of septations and organisation of the infected space. It is notable that fibrinolytic drugs also stimulate excessive pleural fluid output, potentially via monocyte chemotactic protein-1 activity within the pleural space [6,7]; a class action that may explain at least some of their efficacy in pleural infection. However, our understanding of how the infected pleural space is cleared by either saline irrigation or fibrinolytics is very limited and is a key area requiring further laboratory and clinical research. Further large-scale randomised studies are now needed to identify the best form of intrapleural therapy for improving key clinical outcomes in pleural infection, such as length of stay, need for surgery and mortality.

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Bobbio A, et al. Epidemiology of spontaneous pneumothorax: gender-related differences. *Thorax* (8)

Reviewed by Robert J Hallifax

Spontaneous pneumothorax (SP) is a common condition but the true incidence has been poorly studied. Frequently quoted estimates of incidence are based on two outdated single-centre studies from the USA [9] and Sweden [10], and one epidemiological study from the UK [11]. These studies report a range of incidence for SP of 18-24 per 100,000 population per annum for men and 1.2-6 per 100,000 for women.

Bobbio et al [8] conducted a study using the French national dataset which collects information on all hospital stays, regardless of duration, in French public and private hospitals. They identified cases where SP was the main diagnosis leading to hospitalisation, with additional data available including associated comorbidities, hospital stay and some treatment modalities. 60,000 hospital admission episodes were captured over a four-year period (2008-11), and this represents the largest epidemiological study of pneumothorax to date. This data found an annual rate of admission for SP of 22.7 per 100,000 population per annum (95% CI 22.4-23.0). However, that taking into account rehospitalisation, the rate was 16.2 per 100 000 which may be a more accurate reflection of the incidence of pneumothorax. The authors were specifically interested in gender and seasonal differences and reported a male to female ratio of 3.3 to 1, consistent with previous studies. Mean age at presentation was higher in women than men (41±19 years (mean, standard deviation) vs. 37±19 years; $p<0.0001$). The peak incidence (presented as percentage of total pneumothoraces) was men was <20 years; whereas in women the peak was delayed and stayed stable until 40 years. Surgical procedures were slightly more common in men than women (24 vs. 23%, $p=0.02$), but this is unlikely to be clinically relevant. A range of surgical interventions were used: Thoracoscopic bleb resection with partial pleural resection or pleural abrasion (52%), pleurodesis (23%) and resection of bullae by thoracotomy (20%).

Secondary spontaneous pneumothorax (SSP) is commonly defined as a pneumothorax in the context of known lung disease. International Coding and Diagnostics (ICD) codes, routinely used in this and other epidemiological datasets, do not distinguish between primary (i.e. no known lung disease) and secondary pneumothorax and therefore rely on co-morbidities also being coded. The proportion of SSP (15% of cases) was surprisingly low in this paper [8], with previous data suggesting SSP should make up around 50% of the total [9-11]. It is unclear whether these differences represent different populations or a problem with the nature of hospital coding; the fact that the authors found SSP to be more common in men than in women (16% vs 13%, $p<0.0001$) as would be expected from previous studies may favour the latter explanation.

Patients with SSP were more likely to be admitted to a surgical unit or an intensive or intermediate care unit compared to those with primary spontaneous pneumothorax (PSP) (36% vs. 26%, and 40% vs. 25%, respectively; both $p<0.0001$). Hospital stay was significantly longer (median 8 days (IQR 5–14) vs. 5 (3–7) days) and patients with SSP were more likely to need surgical treatment than those with PSP (33% vs. 23%; $p<0.0001$). Clusters of presentations with SP have been reportedly associated with changes in atmospheric pressure and temperature, and thunderstorms [12]. Seasonal variation was not seen in this study [8], although as the data was analysed monthly (for the whole country) it would have required local daily weather data to identify any clustering.

Without good quality prospective studies, accurate recurrence data for SP has been elusive. Data to date has relied upon case series and control arms of randomised controlled trials of PSP, suggesting a recurrence risk of anywhere between 17 and 49% [13-15]. This study [8] reports 28% of patients had more than one pneumothorax-related admission over the 4-year study period. Rehospitalisation rates were higher in SSP.

The limitations of this study [8] are related to the nature of the dataset: reporting hospital admissions related to SP only (and thereby possibly underreporting those individuals managed without hospitalisation); being reliant upon the hospital coding system to define comorbidities and treatments; and a lack of detailed demographic data. Nonetheless, this represents the largest published epidemiological dataset providing much needed data on SP. Patients with SSP have longer hospital stay and are more likely to be admitted to higher dependency units. The aetiology of PSP remains poorly understood. Why patients with supposedly “normal” lungs (or at least “the absence of known lung disease”) should develop a pneumothorax needs to be further explored. Further large-scale prospective studies including good quality phenotypic and (potentially) genotypic data are required to further characterise the aetiology of SP, and determine optimal management strategies.

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Zalcman G, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. *Lancet* (16)

Reviewed by Ioannis Psallidas

Malignant pleural mesothelioma (MPM) is a primary cancer of the pleural space. It is associated with previous asbestos exposure, with a latency period of approximately 30-50 years between fibre exposure and disease presentation [17,18]. Prognosis with MPM is poor and median survival ranges from 12-36 months for localised disease to 8-14 months for advanced disease. Chemotherapy is the only treatment modality that has been shown to improve survival. In 2003 two pivotal phase III trials were published that altered the landscape of chemotherapy in MPM. Standard treatment for unresectable disease since has been combination chemotherapy with cisplatin and pemetrexed [19,20].

Despite many attempts, no subsequent regimen has further improved survival. Current research has tried to exploit some of the common molecular pathways in MPM, with vascular endothelial growth factor (VEGF) thought to play a key role by promoting angiogenesis and tumour growth [21,22]. The addition of bevacizumab (an anti-VEGF monoclonal antibody) to gemcitabine plus cisplatin in the treatment of MPM has been tested in a previous phase 2 study with negative results [23]. Possible explanations for this result could have been an underpowered design due to long survival in the control group; and a large proportion of patients in both groups going on to receive second-line pemetrexed, which may have served to mask any benefit from bevacizumab.

Zalcman et al conducted a randomised controlled open label phase 3 clinical trial to assess the effect on survival of bevacizumab when added to present standard chemotherapy [16]. Patients with performance status (ECOG) 0-2 who were expected to live more than 12 weeks with unresectable MPM were randomised to cisplatin and pemetrexed with or without bevacizumab. The study was open from 2008-2014, randomising 448 patients from 73 hospitals in France. Overall survival was improved in those who received bevacizumab in addition to standard combination chemotherapy, at 18.8 months with bevacizumab versus 16.1 months without (hazard ratio 0.77, 95% CI 0.62–0.95; $p=0.0167$). Early all-cause mortality was similar between the groups: five (2.8%) of 178 patients without bevacizumab versus eight (4.9%) of 164 patients with bevacizumab. Even though fewer patients in the bevacizumab group went on to receive post study chemotherapy: 62.0% (129/208) in the bevacizumab group versus 72.4% (152/210) in the control group, the overall survival with bevacizumab was longer. It should also be noted that that patient subgroups that have previously shown poor prognosis such as ECOG status of 2, haemoglobin concentration ≤ 140 g/L, thrombocytosis, leucocyte count $\geq 8.3 \times 10^9$ /L and sarcomatoid or mixed histology all had overall survival increases with the three-drug regimen.

There was a 31.1% increase in haemorrhages in the bevacizumab group although they were mainly minor epistaxis. Grade 3–4 adverse events (severe or life threatening or causing death) were more common in the bevacizumab group (158 of 222 patients) than in the non-bevacizumab group (139 of 224 patients), and more patients stopped first-line treatment because of toxic effects in the bevacizumab group (53 of 218 patients) than in the non-bevacizumab group (13 of 217; difference 18.3% (95% CI 11.7–24.9)). However, cessation of therapy appeared to have no significant impact on quality of life measures.

The authors also explored the use of VEGF as a prognostic or predictive biomarker in patients with mesothelioma. Baseline serum concentrations of VEGF were assessed on both treatment groups. High VEGF levels on correlated with a worse progression free survival and overall survival. On the prediction analysis the interaction between VEGF levels and treatment groups was not significant. These findings

need further validation on different patients cohorts in order to establish the use of VEGF as a prognostic biomarker.

There are limitations to this study [16], in particular the open label design. Of note, the prescribed dose of bevacizumab of 15 mg/kg was higher than that used for other malignancies, and the use of longer-term bevacizumab in the intervention arm may have impacted on survival in comparison to patients on standard care who did not receive any maintenance chemotherapy. Additionally, the majority of patients had thoracoscopy as a diagnostic procedure with >90% successful pleurodesis. This may have had a positive impact on quality of life measures, and potentially efficacy of and fitness for chemotherapy, through the prevention of pleural fluid recurrence. How this might affect a direct comparison with previous landmark studies [19,20] is equally unclear.

Overall, the results of this study have important implications, demonstrating clear survival benefit from a chemotherapy regimen in a selected patient population. The three-drug regimen should now be considered the standard of care for selected patients with MPM who do not have contraindications to bevacizumab, although its applicability may be limited by financial cost. Further research should continue to inform patient selection for and the best way to utilise this treatment.

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