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Pleural Diseases: Saline Irrigation in Pleural Infection, Epidemiology of Pneumothorax, and Bevacizumab in Mesothelioma

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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 reported in large randomized trials and case series are a 1-year mortality of around 20% and an average length of hospital stay of more than 2 weeks. Medical therapy (broad-spectrum antibiotics and tube thoracostomy) fails in up to one-third of patients, and these patients 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 been 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 loculations develop (2). Combination intrapleural therapy with tissue plasminogen activator and DNase may have a positive influence on relevant clinical outcomes (5, 6), but it 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 centers, albeit in the absence of randomized data or standardized guidance.

Hooper and colleagues (1) performed 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 randomized to either standard chest drain care (30-ml saline flushes three times daily to maintain tube patency) or pleural irrigation (250 ml of saline via gravity administration through the chest tube three times daily) over a 3-day period. Patients were stratified according to the hemithorax volume of the pleural collection (greater or less than 25% on the basis of baseline computed tomographic [CT] evaluation) and the presence of loculation visualized by 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 scans of the thorax from the time of randomization (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 seen on CT scans at Day 3 than those receiving standard care (32.3%; interquartile range [IQR], 19.6 to 43.7%; vs. 15.3%; IQR, –5.5 to +28%; $P < 0.04$). Of the secondary outcomes, the patients who received irrigation were less likely to require surgical intervention for pleural infection (odds ratio, 7.1; 95% confidence interval [CI], 1.23–41.0; $P = 0.03$), but there was no significant difference in any other parameter assessed (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). 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

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a reduction in the size of residual collection and the subsequent need for surgical referral in patients with pleural infection when compared with 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 <3 mmol/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, although 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 scan that 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 that 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 organization 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, 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 randomized 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. ■

References

- Hooper CE, Edey AJ, Wallis A, Clive AO, Morley A, White P, Medford AR, Harvey JE, Darby M, Zahan-Evans N, *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* 2015;46:456–463.
- Corcoran JP, Wrightson JM, Belcher E, DeCamp MM, Feller-Kopman D, Rahman NM. Pleural infection: past, present, and future directions. *Lancet Respir Med* 2015;3:563–577.
- Grijalva CG, Zhu Y, Nuorti JP, Griffin MR. Emergence of parapneumonic empyema in the USA. *Thorax* 2011;66:663–668.
- Maskell NA, Davies CW, Nunn AJ, Hedley EL, Gleeson FV, Miller R, Gabe R, Rees GL, Peto TE, Woodhead MA, *et al.*; First Multicenter Intrapleural Sepsis Trial (MIST1) Group. U.K. controlled trial of intrapleural streptokinase for pleural infection. *N Engl J Med* 2005;352:865–874. [Published erratum appears in *N Engl J Med* 2005;352:2146.]
- Rahman NM, Maskell NA, West A, Teoh R, Arnold A, Mackinlay C, Peckham D, Davies CW, Ali N, Kinnear W, *et al.* Intrapleural use of tissue plasminogen activator and DNase in pleural infection. *N Engl J Med* 2011;365:518–526.
- Piccolo F, Pitman N, Bhathnagar R, Popowicz N, Smith NA, Brockway B, Nickels R, Burke AJ, Wong CA, McCartney R, *et al.* Intrapleural tissue plasminogen activator and deoxyribonuclease for pleural infection: an effective and safe alternative to surgery. *Ann Am Thorac Soc* 2014;11:1419–1425.
- Lansley SM, Cheah HM, Varano Della Vergiliana JF, Chakera A, Lee YC. Tissue plasminogen activator potentially stimulates pleural effusion via a monocyte chemotactic protein-1-dependent mechanism. *Am J Respir Cell Mol Biol* 2015;53:105–112.

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 its true incidence has been poorly studied. Frequently quoted estimates of incidence are based on two outdated single-center studies done in the United States (9) and Sweden (10), as well as one epidemiological study done in the United Kingdom (11). The researchers in these studies reported incidence ranges for SP of 18–24 per 100,000 population per annum for men and 1.2–6 per 100,000 for women.

Bobbio and colleagues (8) conducted a study using the French national dataset, which includes 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 hospitalization, with additional data available, including associated comorbidities, hospital stay, and some treatment modalities. A total of 60,000 hospital admission episodes were captured over a 4-year period (2008–2011), and this represents the largest epidemiological study of pneumothorax to date. These researchers found an annual rate of admission for SP of 22.7 per 100,000 population per annum (95% CI, 22.4–23.0). However, taking into account rehospitalization, 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 sex and seasonal differences and reported a male-to-female ratio of 3.3 to 1, consistent with previous studies. The mean age at presentation was higher in women than in men (mean $\pm$ SD, 41 $\pm$ 19 yr vs. 37 $\pm$ 19 yr; $P < 0.0001$). The peak incidence (presented as percentage of total pneumothoraces) in men was before age 20 years, whereas in women, the peak was delayed and stayed stable until 40 years. Surgical procedures were slightly more common in men than in women (24% vs. 23%; $P = 0.02$), but this is unlikely to be clinically relevant. A range of surgical interventions were used: thorascopic 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 Classification of Diseases 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 comorbidities also being coded. The proportion of SSP (15% of cases) was surprisingly low in this paper (8), with previous data suggesting that 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 on the basis of previous studies, may favor the latter explanation.

Patients with SSP were more likely to be admitted to a surgical unit or an intensive or intermediate care unit than were 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 [IQR, 5–14] d vs. 5 [3–7] d), 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, as well as with thunderstorms (12). Seasonal variation was not seen in this study (8), although because the data were analyzed monthly (for the whole country), local daily weather data would have been required to identify any clustering.

Without good-quality prospective studies, obtaining accurate recurrence data for SP has been elusive. Data reported to date are based on case series and control arms of randomized controlled trials of PSP, suggesting a recurrence risk of anywhere between 17 and 49% (13–15). The researchers in this study (8) reported that 28% of patients had more than one pneumothorax-related admission over the 4-year study period. Rehospitalization rates were higher among patients with 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 hospitalization), 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 stays and are more likely to be admitted to higher-dependency units. The etiology 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 characterize the etiology of SP and to determine optimal management strategies. ■

References

8. Bobbio A, Dechartres A, Bouam S, Damotte D, Rabbat A, Régnard JF, Roche N, Alifano M. Epidemiology of spontaneous pneumothorax: gender-related differences. *Thorax* 2015;70:653–658.
9. Melton LJ III, Hepper NGG, Offord KP. Incidence of spontaneous pneumothorax in Olmsted County, Minnesota: 1950 to 1974. *Am Rev Respir Dis* 1979;120:1379–1382.
10. Bense L, Eklund G, Wiman LG. Smoking and the increased risk of contracting spontaneous pneumothorax. *Chest* 1987;92:1009–1012.
11. Gupta D, Hansell A, Nichols T, Duong T, Ayres JG, Strachan D. Epidemiology of pneumothorax in England. *Thorax* 2000;55:666–671.
12. Alifano M, Forti Parri SN, Bonfanti B, Arab WA, Passini A, Boaron M, Roche N. Atmospheric pressure influences the risk of pneumothorax: beware of the storm! *Chest* 2007;131:1877–1882.
13. Schramel FM, Postmus PE, Vanderschueren RG. Current aspects of spontaneous pneumothorax. *Eur Respir J* 1997;10:1372–1379.
14. Chen JS, Chan WK, Tsai KT, Hsu HH, Lin CY, Yuan A, Chen WJ, Lai HS, Yang PC. Simple aspiration and drainage and intrapleural minocycline pleurodesis versus simple aspiration and drainage for the initial treatment of primary spontaneous pneumothorax: an open-label, parallel-group, prospective, randomised, controlled trial. *Lancet* 2013;381:1277–1282.
15. Massongo M, Leroy S, Scherpereel A, Vaniet F, Dhalluin X, Chahine B, Sanfiorenzo C, Genin M, Marquette CH. Outpatient management of primary spontaneous pneumothorax: a prospective study. *Eur Respir J* 2014;43:582–590.

Zalcman G, et al.; French Cooperative Thoracic Intergroup (IFCT). 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 fiber exposure and disease presentation (17, 18). Prognosis with MPM is poor, and median survival ranges from 12–36 months for localized disease to 8–14 months for advanced disease. Chemotherapy is the only treatment modality that has been shown to improve survival. In 2003, results of two pivotal phase III trials were published that altered the landscape of chemotherapy in MPM. Standard treatment for unresectable disease since then has been combination chemotherapy with cisplatin and pemetrexed (19, 20).

Despite many attempts, no subsequent regimen has further improved survival. Current researchers have 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 tumor growth (21, 22). The addition of bevacizumab (an anti-VEGF monoclonal antibody) to gemcitabine plus cisplatin in the treatment of MPM was tested in a previous phase II study with negative results (23). Possible explanations for this result could be an underpowered design due to long survival in the control group, as well as 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 and colleagues conducted a randomized, controlled, open-label phase III clinical trial to assess the effect on survival of bevacizumab when added to present standard chemotherapy (16). Patients with Eastern Cooperative Oncology Group performance status of 0–2 who were expected to live more than 12 weeks with unresectable MPM were randomized to cisplatin and pemetrexed with or without bevacizumab. The study was open from 2008 to 2014, with researchers randomizing 448 patients at 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: 5 (2.8%) of 178 patients without bevacizumab died as compared with 8 (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 of 208] in the bevacizumab group vs. 72.4% [152 of 210] in the control group), the overall survival with bevacizumab was longer. It should also be noted that patient subgroups which have previously shown poor prognosis, such as an Eastern

Cooperative Oncology Group status of 2, hemoglobin concentration less than or equal to 140 g/L, thrombocytosis, leukocyte count greater than or equal to $8.3 \times 10^9/L$, and sarcomatoid or mixed histology, all had overall survival increases with the three-drug regimen.

There was a 31.1% increase in hemorrhages in the bevacizumab group, although these hemorrhages were mainly minor epistaxis. Grades 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 nonbevacizumab 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 nonbevacizumab 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 in both treatment groups. High VEGF levels correlated with worse progression-free survival and overall survival. In the prediction analysis, the interaction between VEGF levels and treatment groups was not significant. These findings need further validation in different patient cohorts 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 survival in comparison to patients receiving standard care who did not receive any maintenance chemotherapy. Additionally, the majority of patients had thoracoscopy as a diagnostic procedure, with greater than 90% successful pleurodesis. This may have had a positive impact on quality-of-life measures, and also potentially on the 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 a 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 this treatment and the best way to use it. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

16. Zalcman G, Mazieres J, Margery J, Greillier L, Audigier-Valette C, Moro-Sibilot D, Molinier O, Corre R, Monnet I, Gounant V, *et al.*; French Cooperative Thoracic Intergroup (IFCT). Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. *Lancet* 2016;387:1405–1414.
17. British Thoracic Society Standards of Care Committee. BTS statement on malignant mesothelioma in the UK, 2007. *Thorax* 2007;62(Suppl 2):ii1–ii19.
18. Scherpereel A, Astoul P, Baas P, Berghmans T, Clayson H, de Vuyst P, Dienemann H, Galateau-Salle F, Hennequin C, Hillerdal G, *et al.*; European Respiratory Society/European Society of Thoracic Surgeons Task Force. Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma. *Eur Respir J* 2010;35:479–495.
19. Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, Gatzemeier U, Boyer M, Emri S, Manegold C, *et al.* Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol* 2003;21:2636–2644.
20. van Meerbeeck JP, Gaafar R, Manegold C, Van Klaveren RJ, Van Marck EA, Vincent M, Legrand C, Bottomley A, Debruyne C, Giaccone G; European Organisation for Research and Treatment of Cancer Lung Cancer Group; National Cancer Institute of Canada. Randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an intergroup study of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada. *J Clin Oncol* 2005;23:6881–6889.
21. Ohta Y, Shridhar V, Bright RK, Kalemkerian GP, Du W, Carbone M, Watanabe Y, Pass HI. VEGF and VEGF type C play an important role in angiogenesis and lymphangiogenesis in human malignant mesothelioma tumours. *Br J Cancer* 1999;81:54–61.
22. Strizzi L, Catalano A, Vianale G, Orecchia S, Casalini A, Tassi G, Puntoni R, Mutti L, Procopio A. Vascular endothelial growth factor is an autocrine growth factor in human malignant mesothelioma. *J Pathol* 2001;193:468–475.
23. Kindler HL, Karrison TG, Gandara DR, Lu C, Krug LM, Stevenson JP, Jänne PA, Quinn DI, Koczywas MN, Brahmer JR, *et al.* Multicenter, double-blind, placebo-controlled, randomized phase II trial of gemcitabine/cisplatin plus bevacizumab or placebo in patients with malignant mesothelioma. *J Clin Oncol* 2012;30:2509–2515.