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SPONTANEOUS PNEUMOTHORAX: WHAT TO DO FIRST?

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Appropriate management of a patient suffering a spontaneous pneumothorax (SP) continues to be debated. Lack of a uniform approach to SP management has been documented¹ and prompted the American College of Chest Physicians (ACCP) to develop their recent guidelines.² More recently the British Thoracic Society (BTS) published an updated version³ of their previous SP guidelines.⁴

The clinician's primary concern upon initial SP patient presentation is what to do first. Observation, aspiration, and chest tube (small or larger bore) placement remain the three initial SP patient management options. Patients with a secondary SP, SSP, should be managed with a chest tube unless the patient has a small pneumothorax (<3cm or <1cm lung collapse, ACCP and BTS, respectively). In the setting of a small SSP, in hospital observation is recommended.^{2,3}

Patients with a small primary SP (PSP) (<3cm and <2cm lung collapse, ACCP and BTS, respectively) should be managed with outpatient observation. Various options are reasonable for patients with a large PSP (≥3cm and ≥2cm lung collapse, ACCP and BTS, respectively). The ACCP guidelines rely on chest tube placement and the BTS guidelines favor simple aspiration. The BTS guidelines recommend aspiration as first line treatment for all PSP requiring an intervention. In support of aspiration, the BTS guidelines rely on three randomized controlled trials assessing aspiration versus chest tube placement in SP patients.³ All three trials suffer design deficiencies, pivotal among them being limited patient enrollment increasing the likelihood of beta error and casting doubt on conclusions regarding any potential superiority of aspiration. The ACCP recommends placement of a chest tube (≤14Fr or 16-22Fr) in the unstable patient with a large pneumothorax and recommends various drainage procedures as acceptable for the stable PSP patient with a large pneumothorax.²

to page 9

From the Editors

We continue to seek to improve our Newsletter and to provide access to more clinicians worldwide. From this issue onwards, we will introduce brief updates on basic science as relevant to clinical pleural management, in an attempt to promote laboratory research in the pleura, which we believe is important for future advances in pleural diseases.

We like to extend a warm welcome to members of the ALAT (Asociacio n Latino Americana del Torax) and the APSR (Asian Pacific Society of Respirology), who will be receiving the International Pleural Newsletter via e-mail. The Newsletter will also be posted on the website of the International Mesothelioma Interest Group (IMIG) in the near future.

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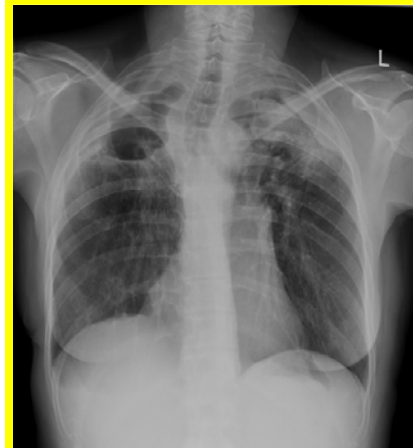
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A Case of Pleuro-Pulmonary Aspergillosis

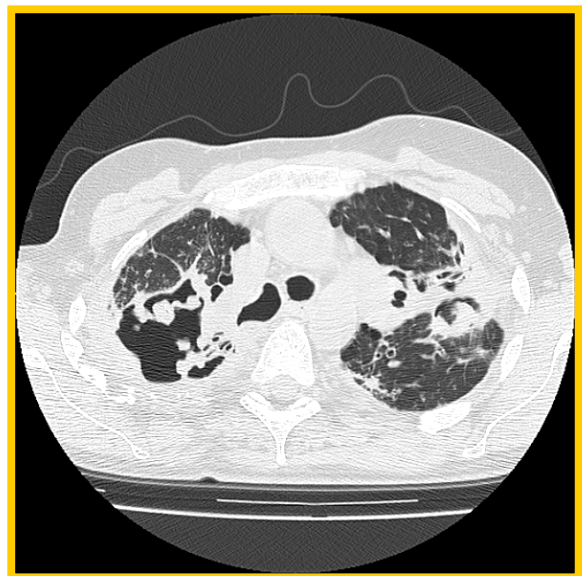
Pleural and pulmonary aspergillosis are notoriously difficult to manage, as illustrated in the following case.

This 53 year old woman had known bilateral apical bullous disease from heavy smoking, and had previously received chemical pleurodesis for recurrent pneumothoraces. Despite that, she suffered from further recurrence of a right-sided pneumothorax, which was treated by surgical pleurodesis with excision of apical bullae. Pleuro-parenchymal aspergillous disease was diagnosed histologically on the resected specimens. Serial radiology showed progressive aspergillus disease in the right pleural space and both upper lobes. She re-presented 12 months later with a



large right broncho-pleural fistula, which failed to respond to conservative management, necessitating a right upper lobectomy and pleurectomy. Post-operatively, she had a persistent air leak which slowly settled with a small residual apical airspace.

Despite long term treatment with itraconazole, she continued to suffer from constitutional symptoms and hemoptysis. Her ESR, aspergillus serology (>7 bands) and total IgE remained significantly raised. Serial imaging showed slowly progressive extensive bilateral pleuro-pulmonary aspergillus disease. CT of the chest demonstrates that the cavity which remained post-lobectomy has been colonized by aspergillus and now has the appearance of an aspergilloma with rounded candle wax like projections from the cavity wall into lumen.



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I favor the use of commercially available 'all-in-one' kits for pneumothorax drainage in any PSP patient requiring drainage and any SSP patient requiring drainage who is not mechanically ventilated. The kits contain various size small bore chest tubes (catheters), ranging from 8Fr to 16Fr,⁵ often accompanied by a one way valve system (eg Heimlich). Many commercial kits offer the option of placement by the Seldinger technique familiar to physicians placing central venous catheters. The kits allow placement of a small bore chest tube (catheter) to effect simple aspiration as described by Light⁶ while offering the opportunity to have a catheter left in place if simple aspiration is unsuccessful, as may be the case in about 25% of PSP and 60% of SSP patients.⁷ This versatility offers both the option of simple aspiration and placement of a small bore chest tube as dictated by the response to aspiration. The BTS terms the use of such devices 'CASP', catheter aspiration of a simple pneumothorax.³ The BTS guideline notes that 'catheter aspiration kits with an integral one way valve system may reduce the need for repeat aspiration'.³ As experience develops with such commercial kits, simple aspiration as described by Dr. Light using a 16-gauge intravenous cannula will likely transition to 'CASP'.

A potential major obstacle hampering adopting CASP may be cost. The cost to the patient of an intravenous cannula at my institution is \$0.55 while that of our commonly used kit (Arrow Cavity Drainage, AK-01601, 14Fr catheter) is \$93. However, the versatility offered by such kits including the increased ease of placement and of sending a patient home with a catheter in place may outweigh the acquisition cost differential.

Meantime, continued research assessing the optimal management of SP patients needs to address initial pneumothorax management and the many other aspects of care about which only limited quality data presently exists. In the interim, the ACCP and BTS guidelines offer well thought out management options that are more alike than different.

¹ Baumann MH, Strange C. The clinician's perspective on pneumothorax management. *Chest* 1997; 112:822-828

² Baumann MH, Strange C, Heffner JE, et al. Management of spontaneous pneumothorax. An American College of Chest Physicians Delphi consensus statement. *Chest* 2001; 119:590-602

³ Henry M, Arnold T, Harvey JE. BTS guidelines for the management of spontaneous pneumothorax. *Thorax* 2003; 58 (suppl II):39-52

⁴ Miller AC, Harvey JE. Guidelines for the management of spontaneous pneumothorax. *BMJ* 1993; 307:114-116

⁵ Baumann MH, Patel PB, Roney CW, et al. Comparison of function of commercially available pleural drainage units and catheters. *Chest* in press

⁶ Light RW. *Pleural Diseases*. Fourth ed. Baltimore: Williams and Wilkins, 2001

⁷ Baumann MH, Strange C. Treatment of spontaneous pneumothorax. A more aggressive approach? *Chest* 1997; 112:789-804

ADVANCES IN BASIC RESEARCH IN PLEURAL DISEASES

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The days when pleural research was limited to studying the cellular and biochemical characteristics of pleural fluids from patient with effusion are long gone. Today, the application of the principles of biophysics, immunology and molecular biology has revolutionized basic science research in pleural diseases.

The use of a confluent monolayer of pleural mesothelial cells (PMC) as an in-vitro model for pleural research is well established and widely used. Pleural homeostasis and integrity can be looked at in an innovative way by measuring the electrical conductance through a monolayer of PMCs. Electric Cell-Substrate Impedance Sensing (ECIS) ¹ provides real time measurement of the strength of the cell to matrix as well as cell to cell adherence and their disturbances in pleural diseases ², giving important insight into the mechanisms of pleural diseases. This, coupled with advanced confocal microscopy imaging and immunohistostaining techniques, allows us to further specify, at the molecular level, the defects in the adhesion and cell attachment mechanisms and their disruptions leading to the formation of pleural effusions during infectious as well as malignant processes ^{3,4}.

The pleural immune response to infections continues to be a major focus of research and study of several groups. Using techniques of molecular biology and applied immunology, researchers are studying the close interactions between PMC and professional immune cells. PMC have been shown to initiate innate immunity by producing chemokines necessary for the trafficking of neutrophils and monocytes to the pleural space in response to infections. They also produce specific instructive cytokines and maintain an effective adaptive immune response.

Animal models of pleural diseases have been developed and are widely used ⁵. Using a CD4 knockout murine model of empyema, Mohammed et al clearly demonstrated an important interplay between the local pleural cells and the systemic immune system, a process essential to produce an effective response and clear the infection.

Perhaps, the most exciting and challenging part of pleural research lies in the clinical application of the knowledge acquired on the bench. The best agent to use in medical pleurodesis is still a subject of intense debate ⁶.

Talc is widely available, inexpensive and relatively safe. It has been successfully used by several chest physicians for medical pleurodesis. Recently, concerns have been raised regarding its safety with a reported risk of ARDS. TGF-beta has been shown to stimulate PMC to produce collagen. In animal models, TGF-beta is at least as effective as talc in inducing pleurodesis ⁷. No human studies have looked at the application of TGF-beta in the management of pleural effusions or pneumothorax. More studies are needed to better define the pleurodesis agent of the 21st century.

¹ Wegener J, Keese CR, Giaever I. Electric cell-substrate impedance sensing (ECIS) as a noninvasive means to monitor the kinetics of cell spreading to artificial surfaces. *Exp Cell Res* 2000; 259:158-66

² Mohammed KA, Nasreen N, Hardwick J, et al. Bacterial induction of pleural mesothelial monolayer barrier dysfunction. *Am J Physiol Lung Cell Mol Physiol* 2001; 281:L119-25

³ Sriram PS, Mohammed KA, Nasreen N, et al. Adherence of ovarian cancer cells induces pleural mesothelial cell (PMC) permeability. *Oncol Res* 2002; 13:79-85

⁴ Ramirez-Icaza C, Mohammed KA, Nasreen N, et al. Disruption Of Mesothelial Cell Focal Adhesions Increases Pleural Permeability. *Am J Respir Crit Care Med* 2002; 165(8):A608.

⁵ Mohammed KA, Nasreen N, Ward MJ, et al. Induction of acute pleural inflammation by *Staphylococcus aureus*. I. CD4+ T cells play a critical role in experimental empyema. *J Infect Dis* 2000; 181:1693-9

⁶ Light RW. Talc for pleurodesis? *Chest* 2002; 122:1506-8

⁷ Lee YCG, Teixeira LR, Devin CJ, et al. Transforming Growth Factor-beta 2 induces pleurodesis significantly faster than talc. *Am J Resp Crit Care Med* 2001; 163:640-4

A BIT OF HISTORY

In 1832, an English physician James Carson demonstrated the creation of artificial pneumothorax in animals, by injecting air into the pleural space with the aim of collapsing the underlying lung, to facilitate its healing. In 1882, Forlanini began applying this technique as a therapy for patients with tuberculosis to promote healing of lung cavitations. Many patients, however, had advanced disease with an obliterated pleural space that would not permit the induction of a pneumothorax, and would eventually be 'consumed' by the disease.

Reference: Entin MA. *Can J Plastic Surg* 1995; Vol 3 (4).

If you have any interesting case of pleural disease to share, or any suggestion and comment on the Newsletter, please contact:

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**6TH MEETING OF THE INTERNATIONAL MESOTHELIOMA INTEREST GROUP
'RECENT ADVANCES IN MESOTHELIOMA'**

& Satellite Meeting: 'Advanced technologies in cancer research - from gene chips to gene therapy.'

The 6th IMIG conference was held from 1-4 December 2002 at the University of Western Australia in Perth, Australia. The three-day meeting brought together researchers in basic science and clinical practice who shared common interests in mesothelioma biology and clinical management. The meeting provided a successful forum for delegates to interact, forging new friendships and establishing future collaborations.

The plenary sessions addressed specific questions relevant to mesothelioma biology. As a new initiative, Key Questions Workshops were conducted to identify important areas in mesothelioma biology for future research. These workshops were very successful with discussion directed at identifying mechanisms underlying mesothelioma development, the status of animal models and pre-clinical trials, the effective use of surgery, identifying new chemo- and radiotherapeutic approaches and host tumor responses and its impact on diagnosis, management and development of new therapies for mesothelioma treatment.

Some highlights from this meeting include presentations by Drs Bruce Case (Canada) and Jim Leigh (Australia) showing that the incidence of mesothelioma was still on the rise and would peak worldwide in 2010. The importance of specific signaling molecules, *Fra-1* and AP-1, in the pathogenesis of mesothelioma was discussed by Dr Brooke Mossman (USA). Dr Luciano Mutti (Italy) demonstrated that agents which switched off PI-3 kinase-AKT HGF-dependent signaling in mesothelioma cells positive for SV40 T antigen increased cell cytotoxicity. Dr Andreas Strasser (Australia) described studies identifying novel pro-apoptotic members of the Bcl-2 family, Bim and Bfm, and Dr Roger Reddel (Australia) discussed how cancer cells prevent cell death by inhibiting telomere shortening through telomerase and alternative lengthening of telomeres. Dr Ken O'Byrne (UK) highlighted the immunoregulatory role of TNF- α in mesothelioma and Dr Joe Trapani (Australia) suggested that engineering T lymphocytes to contain co-stimulatory signals may be used therapeutically to treat mesothelioma patients. Dr Bruce Robinson (Australia) presented data showing that serum mesothelin levels may prove useful for screening asbestos-exposed individuals for the early diagnosis or likelihood of developing mesothelioma. Drs Hedy Kindler (USA), Duncan Stewart (UK) and Hugo Schouwink (Netherlands) suggested the use of computer assisted measurement techniques, contrast-enhanced magnetic imaging and cervical mediastinoscopy to evaluate tumor burden in patients, in particular those considered candidates for surgical based therapy. Drs Paul Baas (Netherlands) and Takashi Nakano (Japan) presented encouraging results from early clinical trials demonstrating positive responses in some patients treated with anti-folates, thalidimide and topoisomerase inhibitors and Dr Bill Musk's (Australia) studies suggest retinol treatment as a possible approach to prevent mesothelioma development. Dr Craig Stevens (USA) demonstrated that localised radiotherapy was successful in treating residual tumor post surgery. Drs Dan Stermann and Steve Albelda (USA) also announced the commencement of phase 1 gene therapy trials using adenoviral vectors containing interferon β genes, based on excellent responses in animal models.

A satellite meeting was held which highlighted recent developments in cancer diagnostics and therapy based on the latest molecular and biochemical technologies such as gene therapy, genomics and proteomics.

For further information about the next IMIG meeting and inclusion on the IMIG mailing list, please contact Dr Steven Mutsaers (IMIG Secretary): mutsaers@aari.uwa.edu.au.

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