

Advances and controversies in pleural diseases

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Pleural effusion is a common presentation for many pulmonary and systemic diseases, particularly heart failure, pneumonia, cancer and tuberculosis (TB). An estimated 1.5 million people develop a pleural effusion each year in the United States alone (1). Despite the prevalence of the disease, research in pleural medicine has attracted far less attention than that of much rarer respiratory conditions. Advances in pleural diseases are desperately lacking and far fewer than in other common pulmonary diseases. One paradigmatic example is the use of talc pleurodesis which was first reported in 1935 (2), but remains the standard therapy for symptomatic malignant pleural effusion in most centers. Few, if any, diseases in medicine are now managed in the same way as they were in the 1930's.

Clinical care of pleural diseases is fragmented among medical specialists, including pulmonologists, thoracic surgeons, internists, intensivists, oncologists, cardiologists and infectious disease physicians. Standardization of practice is therefore difficult, and treatment of pleural effusions can vary significantly. The variations in clinical care of pleural diseases are in part due to the lack of high quality research to guide practice. It is therefore heartening to see a growing amount of research in pleural diseases, including large randomized trials, to address crucial questions. In any scientific exploration journey, the discovery of knowledge raises questions and promotes healthy debates on new controversies. In this special issue of the *Journal of Thoracic Diseases*, leading pleural specialists have provided reviews on the latest advances and controversies in pleural medicine.

The typical example of variations in clinical practice can be illustrated in the day-to-day management of

malignant pleural diseases. When a patient presents with a malignant effusion, they may receive any of a wide range of therapeutic approaches: palliation only (e.g., opioids), observation to see if there is a response to chemotherapy, repeated thoracenteses, surgical pleurodesis (e.g., from talc poudrage to pleurectomy), bedside pleurodesis with various sclerosants (e.g., talc, doxycycline, silver nitrate, iodopovidone, etc.), and placement of an indwelling pleural catheter (IPC) or a pleuro-peritoneal shunt. The use of IPCs has revolutionized the management of malignant effusions. Originally recommended as a fallback option in cases of unsuccessful pleurodesis or lung entrapment, a growing body of evidence supports their use as a first-line treatment in lieu of traditional pleurodesis procedures (3). In this pleural review series, Fortin and Tremblay addressed the contemporary arguments comparing the pros and cons of IPC treatment with conventional pleurodesis (4). Agalioti *et al.* in a separate review, have also highlighted recent recognition of the importance of pleural involvement in lung cancer patients in determining their outcome and therapeutic approaches (5). The ultimate goal, however, of malignant effusion management will be to 'switch off' fluid formation without the need for drainage or pleurodesis. Considerable effort has been expended on uncovering the mechanistic pathway of malignant effusions and identifying therapeutic targets. These advances have been summarized in the review by Spella *et al.* (6).

Recent years have seen pleural medicine being recognized as a sub-specialty in its own right (7). The growing number of procedures (e.g., pleural ultrasound, pleuroscopy, placement of IPCs) and continual discovery

of new treatments (e.g., intrapleural fibrinolytic therapy) have made pleural medicine a vibrant and exciting new arena, best managed by clinicians dedicated to the field. A specialist pleural service raises the profile, and thus the standard of care, of pleural patients and ensures effective management delivered at the highest safety level. The pleural service provides the ideal place for training in pleural procedures and clinical research.

One of the driving forces of developing a pleural service is the recognition that pleural procedures are invasive and associated with potential (including fatal) complications. In this pleural review series, Corcoran *et al.* (8) discuss the range of pleural procedural complications and the various approaches to minimize them. One of the essential components of a rapid-response pleural service is provision of bedside ultrasonography (9). The ability to detect, quantify and characterize the pleural fluid and any adhesions have significantly improved clinical care. Bedside ultrasonography is now considered mandatory in many centers before pleural procedures to enhance safety. Imaging-guidance also allows a less invasive approach for obtaining pleural tissues and reduces the need (and thus morbidity) for surgical or medical thoracoscopy. The former have demonstrated diagnostic yields approaching those of the latter, but may only be feasible when pleural thickening or nodularity exists (10,11). Dixon *et al.* in their review, have detailed the advantages and limitations of imaging-guided biopsy techniques and conventional thoracoscopic approaches (12).

Similarly, advances in intrapleural therapy have significantly reduced the need for surgical treatment of pleural infections. The exciting progress in tPA/DNase therapy has been reviewed by Piccolo *et al.* (13). This practice is now being rapidly adopted worldwide since the publication of the initial randomized trial showing its efficacy (14). Large series have confirmed that over 90% of patients can be successfully managed using this regimen without surgery (15). However, numerous questions remain in our understanding of the pathogenesis of pleural infection; further advances will depend on knowledge that arises from research on these fundamental issues. For decades (if not centuries) we have accepted that pleural infection is always secondary to pneumonia. Questions have been raised as to whether this view is over-simplistic. These questions and their implications have been summarized by McCauley and Dean in this expert review (16).

Another significant pleural infection worldwide is tuberculous pleuritis, and its best management is discussed

by Vorster *et al.* (17). Since first reported in 1978 (18), pleural fluid adenosine deaminase (ADA) has substituted blind pleural biopsy in many TB endemic areas (19). In the era of multidrug resistant TB, neither ADA nor the finding of pleural granuloma from tissue biopsy provides sensitivity data of the mycobacteria. Advances in liquid culture media and other means to capture mycobacteria need exploration (20).

Research in pleural diseases is now growing and large-scale trials will help answer many clinical practice questions. Some ongoing studies include the SMART trial on prophylactic radiotherapy for procedural tract metastases in mesothelioma (21); the TAPPS trial to compare talc poudrage versus talc slurry pleurodesis (22); the AMPLE trial that compares IPC with talc pleurodesis (23); and the IPC-PLUS study which examines whether combining talc pleurodesis with IPC may provide improved pleural symphysis rates over those of IPCs alone (24). Multi-center collaborations for prospectively collected data have helped generate prognostic factors in malignant pleural effusions (LENT score) (25) and in pleural infection (RAPID score) (26). Further major breakthroughs, however, will have to rely on better understanding of the pathobiology of pleural diseases. This review series has included state-of-the-art articles on mesothelial cell biology (27), and the use of microRNA in mesothelioma (28). These and other major areas of research in basic sciences in pleural diseases will form the platform for future advances.

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