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Pleural Effusions and Pneumothorax: Beyond simple plumbing

Expert opinions on knowledge gaps and essential next steps

Authors:

Rajesh THOMAS [1,2] MBBS PhD FRACP
rajesh.thomas@health.wa.gov.au

Najib M RAHMAN [3] MA DPhil FRCP
najib.rahman@ndm.ox.ac.uk

Nick A MASKELL [4] MD FRCP
Nick.Maskell@bristol.ac.uk

Y C Gary LEE [1,2,5] MBChB PhD FRACP FCCP FRCP
gary.lee@uwa.edu.au

Affiliations:

[1] Department of Respiratory Medicine, Sir Charles Gairdner Hospital, Perth, Australia.

[2] Pleural Medicine Unit, Institute for Respiratory Health, Perth, Australia.

[3] Oxford Centre for Respiratory Medicine, Churchill Hospital, Oxford and Oxford NIHR Biomedical Research Centre, UK.

[4] Academic Respiratory Unit, Department of Clinical Sciences, University of Bristol and North Bristol Lung Centre, North Bristol NHS Trust, Westbury on Trym, UK.

[5] Centre for Respiratory Health, School of Medicine, University of Western Australia, Perth Australia.

Corresponding author:

Prof Y C Gary LEE, School of Medicine, UWA, 533 Harry Perkins Building, QE II Medical Centre, Perth, WA 6009, Australia. Tel: +61 8 61510913; Fax: +61 8 64572816.

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Pleural Effusions and Pneumothorax: Beyond simple plumbing

Abstract

Pleural diseases affect millions of people worldwide. Pleural infection, malignant pleural diseases and pneumothorax are common clinical challenges. A large number of recent clinical trials have provided an evidence-based platform to evaluate conventional and novel methods to drain pleural effusions/air which reduce morbidity and unnecessary interventions. These successes have generated significant enthusiasm and raised the profile of pleural medicine as a new subspecialty. The ultimate goal of pleural research is to prevent/stop development of pleural effusions/pneumothorax. Current research studies mainly focus on technical aspects of pleural drainage. Significant knowledge gaps exist in many aspects such as understanding of the pathobiology of the underlying pleural diseases, pharmacokinetics of pleural drug delivery etc. Answers to these important questions are needed to move the field forward. This article collates opinions of leading experts in the field in highlighting major knowledge gaps in common pleural diseases to provoke thinking beyond pleural drainage. Recognizing the key barriers will help prioritize future research in the quest to ultimately cure (rather than just drain) these pleural conditions.

1. Introduction

Pleural diseases affect millions of people a year worldwide(1, 2) but their management has received little attention for centuries. Common treatments are often based on unproven concepts. Recent years have seen growing recognition of the importance of pleural research which has significantly improved care. Clinical trials have disproved many conventional practices by showing no benefits (eg streptokinase for pleural infection) or even harm (eg radical surgery for mesothelioma). New and exciting therapies have also emerged, eg for pleural infection. Most recent pleural studies have focussed on 'pleural plumbing', i.e. evacuation of effusions or pneumothorax. They have immediately impacted daily practice, generated significant enthusiasm and put pleural medicine in an unprecedentedly high profile.

While there is no question optimal pleural drainage advances care, the ultimate goal of pleural research must be *to stop the development of the effusion or pneumothorax* in the first place. However, the pathobiology of the underlying pleural diseases remains obscure and must now be the focus of the next 'wave' of pleural research.

The recent advances in pleural research has been summarized by many reviews and has stimulated the development of many clinical guidelines recently published or in progress. This article collates opinions of leading experts in the field in highlighting the major knowledge gaps in common pleural diseases, particularly malignant pleural effusion (MPE), mesothelioma, pleural infection and pneumothorax, to provoke thinking beyond pleural drainage. Recognizing the key barriers will help prioritize future research in the quest to ultimately cure (rather than just drain) these pleural conditions.

2. Why have we not cured pleural infection?

Pleural infection remains a common disease with recent epidemiological studies showing increasing rates in all age groups(3). Two studies, the Multicentre Intrapleural Sepsis Trial (MIST)-1 and -2, have taught us that intrapleural streptokinase has no benefit in reducing mortality or need for surgery(4), whereas combined intrapleural tissue plasminogen activator (tPA)/deoxyribonuclease (DNase) therapy improves pleural drainage and hastens resolution of sepsis(5). tPA/DNase therapy has not been directly compared previously with standard surgery in pleural infection; however, there are now over 600 reported cases of successful use of intrapleural tPA/DNase therapy in pleural infection and it has become standard front-line treatment in many centres when chest tube drainage alone has not cleared the pleural collection and systemic signs of infection remain. Details on tPA/DNase use(5) and other clinical advances have been summarized elsewhere(6, 7). These findings are particularly important in patients unfit for surgery. However, despite advances in the field over the past decade, the mortality rate has not significantly improved.

A large number of unanswered questions, that hamper our progress in providing better therapy for pleural infection, still remain (8). Currently we group all pleural infection cases under the same broad banner. However, patients with pleural infection are heterogeneous in their comorbidities, causative organisms, and infected pleural fluid characteristics. Better biomarkers to predict the clinical course, response to antibiotics (with/without drainage) and the need for invasive treatment strategies will be helpful. It would be interesting to explore if the RAPID score(9), prospectively validated for predicting mortality in pleural infection, can also be extended to guide management strategies and improve outcomes.

Antibiotics and pleural drainage (be it aspiration, chest tube or surgery) are the two cornerstones of management but most research have focussed on the latter. Limited data exist on the pharmacokinetics of pleural concentration of antibiotics. We have little knowledge whether antibiotics administered systemically achieve minimal inhibitory concentrations (MIC) in the pleural space necessary for common pathogens. It was shown only recently that bacteria can thrive in both the pleural fluid(10) and pleural tissue(11). Antibiotics must therefore adequately penetrate both compartments to control infection. The current practice of giving intravenous antibiotics followed by oral agents for 2-4 weeks after discharge is empirical with no robust data in its support and should be a focus of further studies.

Effective antibiotic therapy may reduce the severity of pleural infection in the first place and/or enhance clearance of infected pleural fluid, thus reducing/negating the need for invasive drainage. Optimal antibiotic strategy, e.g. route of drug delivery and duration, can only be established when we can measure antibiotic penetration to pleural tissue and fluid. Also, appropriate choice of antimicrobials has to be guided by the causative organism(s) but only approximately one of every three cases had a positive microbiological culture(12). Better methods to identify causative organisms in pleural infections are desperately required.

Conventional teaching states that infected pleural fluid must be drained, usually with a chest tube at presentation or surgery when chest tube drainage fails. However, many localised infections (e.g. lung abscesses) are successfully treated with antibiotics without drainage. Infected pleural collections in inaccessible areas, e.g. fissural and mediastinal pleural collections, can also resolve with systemic antibiotics alone. Separating patients who require drainage from those who can be conservatively managed will be a great step forward. Controversies still remain, e.g. whether the residual pleural thickening that persists after sepsis

resolution can cause chronic breathlessness. Whether, and when, thoracic surgery is needed in this setting has not been addressed either by high quality clinical trials.

Preventing bacterial invasion of the pleura in the first place remains the ideal goal. However, we have yet to understand how organisms invade the pleural cavity. Some bacteria enter as a consequence of a pneumonic illness, some via hematogenous spread and some translocate from oral pharyngeal flora. Why some patients with pneumonia develop parapneumonic effusions when most do not, and why some bacteria (e.g. *Streptococcus milleri* group) invade the pleura more commonly than others (e.g. *Hemophilus influenzae*) remain unexplained.

The belief that parapneumonic effusion is an exaggerated pleural inflammatory response challenges our traditional thinking but is supported by a randomized clinical trial (RCT) of systemic steroids in paediatric empyema(13) and a cohort study of adult patients with pleural infection treated with inhaled corticosteroids(14). An exploratory placebo controlled RCT on dexamethasone in adults with parapneumonic effusion is underway(15). Animal studies, the logical first step to address these important questions, have not contributed significantly. The spectrum of bacteria causing pneumonia in mice and rabbits are different from that in humans. This may be because the thin visceral pleural membrane of mice and rats probably permits easier bacterial migration than does the thicker visceral pleura in humans.

These important questions need to be answered for the field to move forward and ultimately reduce the incidence and mortality of this important and common disease.

3. Why have we not cured malignant pleural mesothelioma?

MPM remains an incurable cancer since its early report in 1960 by J C Wagner(16). The global incidence of mesothelioma has been increasing since and the World Health Organization predicts a major rise of the disease in developing countries over the next few decades(17). Although research efforts have provided valuable information on the biology of mesothelioma, no therapeutic advances have made a realistic impact on the dismal survival rates (median 12 months). To date, only three RCTs of mesothelioma have shown survival benefits, all modest. RCTs on the use of pemetrexed (or raltitrexed) and platinum duplet have shown benefits in survival, but by less than three months(18, 19). Addition of bevacizumab further prolongs survival by similar margins but at the expense of more side effects (especially vascular/thrombosis and bleeding)(20). Hence the latter has not become standard practice in most countries. Numerous other agents have been tested and many more are underway (see review(21)). Although several had shown promise in phase II studies(22), none were found to have survival benefits in randomized trials(23-25). This is in part due to the selection bias of recruiting fitter patients with more stable disease for novel trials and it highlights the importance of placebo-controlled randomized studies.

It was cleverly said (by Prof Bruce Robinson, University of Western Australia) that if mesothelioma is a lesion that grows on the forehead, we would have found a cure by now. This sums up the challenges (described below) in conquering mesothelioma.

To begin with, MPM develops in the hidden pleural cavity which makes early detection extremely difficult. MPMs are often characterized by a large number of tiny pleural nodules which escape easy detection by current imaging modalities. Some cases of mesothelioma develop as diffuse pleural thickening which again is difficult to differentiate by imaging alone, without tissue biopsy, from benign pleural plaques and non-asbestos causes of pleural fibrosis.

By the time patients present with a pleural effusion (the most common initial presentation in mesothelioma), the tumour is well advanced and usually spread throughout the pleural surface.

These characteristics of mesothelioma mean that complete tumour resection is impossible even with radical treatments such as extra-pleural pneumonectomy (± chemo-radiation). Indeed, the MARS randomized trial found that extra-pleural pneumonectomy was harmful and shortened survival by 5½ months compared to patients who were not operated upon(26). Pleurectomy/decortication, a less aggressive form of surgery aimed at debulking pleural mesothelioma, was trialled in another RCT; the study found that pleurectomy/decortication had no survival benefit over standard talc pleurodesis but incurred more post-operative complications(27). Radiotherapy with curative intent is not practical at safe doses given the large surface area of the parietal, visceral and diaphragmatic pleura involved.

Monitoring of disease progress and repeated sampling of tumour tissues are also difficult in MPM because of the need for repeated invasive interventions to access the pleural space.

A reliable biomarker would be ideal to help overcome some of these challenges, and may assist in early disease detection, diagnosis, and monitoring of disease response/progress. Many potential markers have been proposed; unfortunately most failed to reproduce the benefits in validation cohorts or other study populations (e.g. osteopontin, fibulin-3)(28, 29). Mesothelin is the only marker that has shown some promise in predicting development of mesothelioma. An elevated mesothelin level (in serum or pleural fluid) is useful and points towards pleural malignancies (most commonly mesothelioma and occasionally, other metastatic carcinomas) but its sensitivity is low(30). A rise in the serum level of mesothelin raises suspicion of development of mesothelioma(31). However, even in that setting, a serum marker would not

be able to point towards the site of mesothelioma development as it can arise from any of the serosal cavities, posing clinical difficulties in surveillance.

One of the (many) hurdles in biomarker development for mesothelioma and in the search of therapeutic agents is the disease heterogeneity. Surgical studies have confirmed that there is a higher chance of finding both sarcomatoid and epithelioid mesothelioma components within any individual patient if more tissue samples are taken(32, 33). Heterogeneity within areas of each tissue component is also highly likely. In future, a combination of biomarkers may be needed. The lack of faithful preclinical models also makes screening for new therapies difficult.

In a disease which has a clear causative factor (i.e. asbestos), eliminating the source should ideally be the best approach. Disappointingly, asbestos continues to be widely mined and used, especially in developing countries because of its low costs and effectiveness as insulation material. Workers in these regions often have poor access to first-world healthcare and mesothelioma is likely to be grossly under-recognized and -reported.

In the developed world, asbestos use was banned decades ago but the incidence of mesothelioma has only plateaued but the predicted decrease in its mortality rates, to date, has failed to materialize(34). One explanation is that inhaled asbestos fibres are often not fully degraded and the longer the individual lives, the more likely he/she will develop mesothelioma. The increased longevity of the population means that more elderly patients, who had exposure from several decades before, will develop mesothelioma. This will offset the decreasing incidence of younger patients with mesothelioma because of the banning of asbestos use in recent decades. The latest USA data support this hypothesis and the resultant stable overall rate of mesothelioma. This changing demographic has significant implications on future drug

development as elderly patients often have concurrent co-morbidities and are unlikely to benefit from aggressive chemo-/immuno-therapeutics.

4. Why have we not cured malignant pleural effusions?

Most MPEs arise from cancer metastasis to the pleura, frequently from lung and breast carcinomas(1). Primary pleural cancers, especially mesothelioma, commonly present with a MPE(35). The goal of care in most cases is symptom palliation(36). Pleurodesis has remained the preferred treatment for MPE since the first published report of talc poudrage in 1935(37).

Recent years have seen many multicentre RCTs on MPE which provided much-needed evidence-based evaluation on pleurodesis techniques and agents. The data provide strong support for less invasive pleural interventions over more aggressive surgical approaches. Bedside pleurodesis using talc slurry has similar outcomes as talc poudrage by VATS or medical thoracoscopy(38, 39). Indwelling pleural catheters (IPC) represents a paradigm shift in MPE treatment and allows long-term ambulatory fluid drainage, improves symptoms and quality-of-life (QoL) whilst reduces hospital days and need for repeated invasive pleural procedures(40-42). However, IPC also has its unique set of complications(43-47). Combining IPC and pleurodesis is therefore an attractive concept. Talc instillation via IPC in MPE patients without non-expandable lung (NEL) improves pleurodesis rate and facilitates early catheter removal(48). These exciting advances have led to the development of several new guidelines on MPE and IPC management(49, 50). Attempts (e.g. OPTIMUM and EPIToME)(51, 52) have been made to further refine methods for IPC-pleurodesis. The AMPLE-3 RCT compares the IPC-pleurodesis approach against VATS pleurodesis in good performance status patients to address the current equipoise.

Although these progresses impact care worldwide, they focus predominantly on the technical aspects of fluid removal. Switching off the pleural fluid production by cancer cells remains the elusive holy grail of MPE research(53). Cancer cells secrete an array of meditators to promote angiogenesis; the resultant hyperpermeability of the neo-vasculature allows plasma extravasation leading to pleural fluid formation(54). Targeting key mediators of angiogenesis and vascular hyperpermeability, e.g. vascular endothelial growth factor, has shown promising results in murine models, but translation into humans has proved challenging(54-56). *In vitro*, malignant pleural fluid promotes cancer cell growth and protects them from chemotherapy effects(57). Novel intra-pleural approaches (e.g. gene therapy) to control the underlying pleural malignancy have thus far been disappointing(58-60). Many reasons may explain the failure in translation: our suboptimal understanding of the pathobiology of fluid formation, differences between humans and preclinical models, backup redundancy in how cancers stimulate fluid production (that bypass blockade of single molecules) as well as the heterogeneity of human MPEs, amongst others.

MPEs encompass a diverse patient group with many different underlying cancers with individual patients differing in their clinical course, treatment response, prognosis and outcome(61). Yet, MPE is often treated as a single entity. To improve care, we need to provide a tailored approach for individual patients. To achieve that, we require better abilities to predict outcomes, such as which patients will (or will not) benefit symptomatically from fluid drainage(62), the likelihood of success or failure/fluid recurrence with different therapies (especially pleurodesis), and survival.

A few individual factors associated with the likelihood of recurrence of MPE after initial therapeutic drainage or pleurodesis, e.g. a high pleural fluid lactate dehydrogenase (LDH) level, low pleural fluid pH and glucose, and a lower Karnofsky performance score. Large series have suggested that only about half of all MPE patients require 'definitive' fluid control(63), but the predictors identified (e.g. low pleural fluid pH, large effusion and higher age) are relatively non-specific(64). Patients' symptoms often correlate poorly with the size of the effusion and up to 25% of patients do not show symptom benefits after fluid drainage(65). Breathlessness in MPE is multifactorial and involves a complex interplay of many organ systems, biomechanics and neurophysiology; a challenging research journey is anticipated in this field(66). Recurrence of MPE also depends on survival; the published LENT (pleural fluid LDH, ECOG performance score, Neutrophil-to-lymphocyte ratio and Tumour type) prognostic score for MPE can be useful(36).

Patients with NEL account for up to a third of all MPE cases and are probably associated with a worse prognosis. These patients are often excluded from RCTs as they are not candidates for pleurodesis. A clinically relevant definition of NEL and the optimal means to its detection and subsequent management are crucial areas that remain under-researched (see our recent editorial)(67).

Identifying the most important patient-relevant treatment outcomes, and developing tools to accurately measure them, has been a focus of recent research(68). The 100-mm visual analogue scale for dyspnoea (VAS-D), a patient-reported outcome measure (PROM) used to quantify breathlessness, has now been adopted in many MPE trials(40, 42). VAS-D is an important step forward, but it bears the same shortcomings of other subjective measures of PROM(69). The same level of breathlessness is likely to be scored differently at different stages of the disease

as individuals adapt their lifestyles to symptoms. The same score may represent very different levels of discomfort to different patients, and are influenced by other factors (e.g. pain, depression, etc). In future, objective measures of PROMs will likely supersede subjective scores. Measurements of patients' physical activity levels, e.g. with accelerometers (actigraphy), is one such approach and is more meaningful to patients than VAS-D scores. Accelerometry represents a composite outcome measure that would capture the overall disease impact of MPE and treatment response on patients' QoL(70).

5. Why have we not cured spontaneous pneumothorax?

Spontaneous pneumothorax is common and traditionally has been differentiated, somewhat artificially, into "primary" or "secondary" pneumothorax depending on the absence and presence of diseased lung respectively(71). Although they have distinct prognoses and outcomes, the broad management goals of prompt re-inflation of collapsed lung, control of persistent air leak and prevention of recurrence are similar and have remained largely unchanged for many decades. Most published studies focus on management of patients who have suffered a pneumothorax. The ultimate goal - to prevent pneumothorax - remains a long way off with large, high-quality epidemiological studies demonstrating an increase in pneumothorax rates across all age groups, including in the elderly(72, 73).

Perhaps the key issue of importance is identification of the factors driving air leak from the visceral pleura which results in pneumothorax. This comes down to an improved understanding of "what is wrong with the lung", a question that can be posed both to primary (PSP) and secondary pneumothorax (SSP) where events can occur in those with diseased lungs of various severities. Scientific assessment of the key differences in pneumothorax and normal lung, in

terms of inflammation, structural integrity, genetic drivers and mechanical forces are required to delineate the key etio-pathogenic stages of pneumothorax development, with a view to targeted treatments in at risk populations to try to reduce this healthcare burden.

Indeed, the pathogenetic lines separating the PSP and SSP entities are increasingly blurred. Whether the underlying lung is indeed "normal" in primary pneumothorax has been challenged. Histologically, lung tissue in PSP often shows 'emphysema-like changes'. On imaging, blebs and bullae are common even in patients with PSP. Whether these changes are causative, or a bystander phenomenon, is debated. When inhaled fluorescein is administered prior to thoracoscopy in patients with PSP, the diffuse presence of fluorescein over the visceral pleura (far beyond the areas of blebs) raises the possibility that air leak in pneumothorax is a diffuse process through pores in the visceral pleura, rather than via a single ruptured bleb/bulla(74).

Identifying underlying causes of pneumothorax is important. Whilst tobacco smoking undoubtedly has a strong association with the development of pneumothorax and its recurrence, the short- and long-term risks associated with marijuana smoking and vaping, and the mechanisms by which they induce pneumothorax, are less clear.

Many known risks are unavoidable, e.g. molecular abnormalities in genetic diseases such as Burt-Hogg-Dube syndrome (folliculin), neurofibromatosis (NF1), Marfan's syndrome (fibrillin-1), Loeys–Dietz syndrome (transforming growth factor beta receptors) and tuberous sclerosis (Cathepsin K). Future work on the role of these molecules in the lung may shed light on the underlying process(75).

What precipitates the pneumothorax, or its recurrence, is equally important and intriguing. If genetic predisposition is the key, then one would expect the incidence of spontaneous pneumothorax to rise from childhood(76) and the cumulative risks to continue to increase over one's lifetime. Instead in large studies, pneumothorax tend to recur more within the first two years after the primary event, suggesting other triggers are at play. Numerous candidates of triggers, from fluctuations in atmosphere pressure to loud music have been proposed(77), none convincingly proven.

It is also increasingly clear that the theory of one-airway, one-hole, one-air leak causing a pneumothorax is over-simplistic. Inter-lobar and intra-lobar collateral ventilation can occur through incomplete fissures in many cases, leading to failure of targeted airway occlusion treatment, e.g. endobronchial valves, in persistent air leak. A better understanding of the anatomical variations (e.g. in air leak sites, airway branching systems, fissural integrity, etc) and the effects of various physiological changes (e.g. lung re-inflation, intra-pleural pressures, intra-thoracic pressures, etc) is needed to guide treatment interventions.

The optimal treatment approach once a pneumothorax has occurred remains controversial. Most guidelines till now advocated prompt removal of the accumulated pleural air using needle or chest tube. The recently published Primary Spontaneous Pneumothorax RCT(78) shows that conservative (observation only) management was adequate in 85% of patients with moderate-to-large PSP(79, 80), sparing patients pleural drainage procedures, time in hospital and surgeries. Intriguingly, observation alone yielded a lower recurrence rate than those whose PSP was drained. One explanation is that the site of air leak in the visceral pleura, like any wound, will heal faster and better if the lung is left deflated and therefore edges of the wound in closest proximity. Reinflating the lung with chest tube drainage improves radiographic appearances but may in actual fact pull the wound further apart and impede healing. These results should

raise interests in further studies on the pathophysiological mechanisms involved in pneumothorax healing.

A proportion of PSP and many of the SSP patients will have a persistent air leak. For these patients and for those who require drainage, the optimal intervention continues to be debated(81). The role of ambulatory management using one-way valves attached to a drainage device was examined in the RAMMP trial. The study (reported in abstract form) suggests the use of ambulatory devices are safe and effective in this setting(82). The ideal approach, especially in those with SSP, who cannot undergo surgical treatment has not been adequately explored. Autologous blood patch, ambulatory drainage devices, portable digital suction devices and endobronchial valves have all been reported but high-quality clinical studies are needed to define the role of each of these approaches in the treatment algorithm.

How best to identify those whose pneumothorax will recur is another challenge. Whether lung health in the longer term is the same as people who have never had a pneumothorax is unknown. Although recurrence rates are currently quoted as between 20% and 30% over a two-year period, a tool to predict recurrence on a personalised basis would be invaluable to guide early preventative treatment.

The demographics of pneumothorax have changed over time, and SSP and iatrogenic pneumothorax now significantly outnumber PSP cases. Research resources and focus should likewise be directed to these subgroups.

6. Into the Future

Major progresses have been made in pleural medicine in the past 25 years which have reduced morbidity and unnecessary/invasive interventions for patients with pleural diseases. Pleural medicine is now respected as a respiratory subspecialty and features regularly as symposium topics in all major pulmonary conferences. The growing number of clinicians entering pleural training ensures the development of the next generation of pleural specialists.

'Prevention is better than drainage' (Figure 1). The focus of pleural research till now has been limited to how to evacuate (malignant or infected) pleural fluid and air. Escalating the scientific level of pleural research beyond 'plumbing' is key to finding new therapeutics that can stop pleural diseases from developing in the first place. It is also an essential next step for pleural medicine to be recognized by the scientific community as a true niche for research.

Addressing the underlying causes of the pleural conditions however is challenging and as such has received far less attention. Heterogeneity in pleural anatomy and susceptibility to disease (e.g. bacterial strains) between human and animals make many preclinical models unreliable. The need to invasively access the pleural cavity and tissues prohibits repeated sampling in many cases. Although the number of clinical researchers has grown, a lack of clinician scientists bridging translational research will continue to present a hurdle to advances in the field.

The challenges and hurdles are substantial but the potential rewards of advancing pleural research are significant, and beyond what is commonly realised. The pleural cavity allows examination of local inflammatory/fibrotic response to a pathogenic challenge (be it infection or cancer). The use of IPCs permits repeated sampling of local response (e.g. to therapeutic agents) and has attracted increasing attention of researchers developing novel pharmaceutical

agents. Pleural fluid is abundant in volume and contains valuable biological material (e.g. cancer cells) for research. The advent of IPC, in particular, represents a unique opportunity for longitudinal sampling of cancer cells from the same patient, otherwise not feasible in these clinical settings. It is highly likely that the findings from pleural research can be extrapolated to other mesothelial cell-lined (i.e. peritoneal and pericardial) cavities. These distinct advantages can help foster commercial interests and funding to support translational research, essential for future advances. Multicentre international collaborations to build large biobanks can help to overcome the challenges of heterogeneity of pleural diseases.

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The Authors:

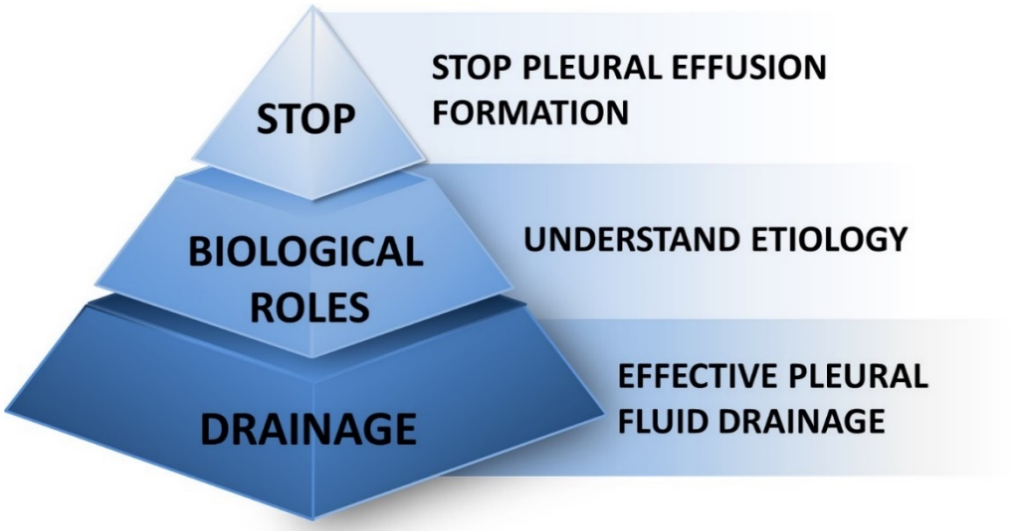

Figure 1 [Reproduced with permission from Respirology(83)]: Recent advances have provided various novel approaches to remove pleural fluid (e.g. indwelling pleural catheter for malignant pleural effusion and tissue plasminogen activator/deoxyribonuclease for pleural infection). The next step to improve care involves developing better understanding of the pathobiology of pleural diseases in order to design new therapeutic approach. The ultimate goal is to prevent/stop the pleural diseases (and associated effusion formation).

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