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EDITORIAL

Empyema as an orphan disease: So many approaches and so few data

In our modern era of medical science characterized by microsatellite arrays and gene therapy, it becomes increasingly challenging to advance the investigative needs of what I call ''high impact orphan diseases.'' These conditions occur commonly, present remarkably high morbidity and mortality, yet receive little if any research funding. Perhaps their common occurrence generates a sense of tolerance to their public health impact and encourages resources to flow toward less ''garden-variety'' conditions that promise cutting edge diagnostics and therapies.

Until recently, chronic obstructive pulmonary disease (COPD) as the fourth leading cause of death worldwide represented one such high impact orphan disease. Now that the National Institutes of Health has initiated a major public awareness campaign to address the epidemic of COPD [1], it may hopefully lose its orphan status.

The future, however, does not look so promising for thoracic empyema. Pleural space infections complicating pneumonia remain common and carry a tremendous global health burden in terms of both morbidity and mortality [2,3]. Patient series report mortality rates between 7 and 33% for hospitalized patients [3—5] with death occurring in more than 50% of the elderly and those with comorbidites [3,5]. Moreover, epidemiologic studies recently established that empyema is on the rise. In the state of Washington in the United States, the incidence rate of empyema has increased by 2.8% *each year* from 1987 to 2004 [6]. Canadian data report an aggregate 12.4% age-adjusted increase in empyema incidence from 1995 to 2003 [7]. Future demographics of an increasing population of older patients, longer survival of patients with comorbidities, and emerging respiratory pathogens with poor drug susceptibility patterns will most likely maintain these worrisome trends.

So empyema is indeed a high impact condition from a public health perspective, but what makes it an orphan disease? In my opinion, inadequate research funding has limited our knowledge of the disease and retarded the development of evidence-based diagnostic and therapeutic algorithms.

Consider the diagnosis of empyema. All existing reports indicate that pleural infections among hospitalized patients admitted with pneumonia remain under diagnosed partly because clinicians under appreciate the importance of early diagnosis and prompt drainage [8—10]. Moreover, no comparative studies with outcome data guide the application of modern chest imaging for selecting patients to receive individualized therapy. The standard chest radiograph is woefully insensitive for detecting pleural fluid (200—500 ml pleural fluid required), yet it remains the most commonly performed screening study for parapneumonic effusions. Ultrasonography (US) represents a major advance in imaging the pleural space with an ability to detect as little as 5 ml of pleural fluid. Most patients at risk for parapneumonic effusions, however, do not get screened with US. Also, although various patterns of US images may have diagnostic implications for pleural space infections [11,12], none has been sufficiently investigated to obviate thoracentesis for patients with parapneumonic effusions. The literature on chest computerized tomography (CT) for pleural infections is similarly characterized by observational and descriptive studies without the robust prospective comparative studies published for other cardiopulmonary conditions, such as pulmonary embolism. Pleural fluid analysis for establishing the need for drainage remains similarly

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ill defined. Professional society guidelines recommend the staging of pleural infections with pleural fluid chemic tests, such as lactate dehydrogenase (LDH) and pH, to aid drainage decisions. The data for pH, however, derive from flawed observational studies, and no outcome data support the proposed cut off points for LDH [13]. The role of procalcitonin in diagnosing pleural infection remains unexamined despite an explosion of research of this biomarker for other infectious conditions.

Research data regarding the therapy of empyema remains almost entirely lacking. No outcome studies guide empiric antibiotic therapy, which perpetuates the adage to direct therapy toward the underlying pneumonia pending pleural fluid culture results. Traditional approaches of blind insertion of a large-bore chest tube by surgical intercostal incisional techniques [14,15] are slowly giving way in some centers to image-guided small-bore pigtail catheter insertion [16,17], but no comparative studies exist and experts still differ regarding the desirability of large-bore [15,18] versus small-bore chest tubes and whether real-time imaging is required [19,20]. Once a catheter is placed for drainage, the duration of drainage before conversion to more aggressive interventions remains debatable with experts recommending from 2 to 7 days [4,21—24] to as long as many weeks [25]. The role of fibrinolytic therapy for loculated effusions is unknown. The Multicenter Intrapleural Sepsis Trial (MIST1) trial [26] represents the only large prospective randomized study of fibrinolysis, but the study's methodology limits generalizability [27]. The study included nonstandardized treatment algorithms without the use of advanced chest imaging. The MIST1 selection of streptokinase for fibrinolysis does not inform present questions regarding the effectiveness of intrapleural recombinant tissue plasminogen activator, which is now more commonly used for empyema drainage [20].

Perhaps most troubling is the absence of adequate studies regarding the role of thoracoscopy or thoracotomy for draining pleural infections. Although many physicians use US or CT imaging to determine the need for primary surgical drainage and the specific surgical technique, recent studies indicate a poor association of imaging results with patient outcomes with therapy [16,28]. Patient selection for and timing of surgical drainage remains a matter of expert opinion and varies widely between institutions.

So what can physicians do in managing this common and important condition for which adequate research remains lacking? I believe we need to first accept our uncertainty and avoid over confidence in our — and our colleagues' — ability to recommend ideal therapy. An adequate evidence base simply does not exist to warrant too much confidence or arbitrary opinions; existing practice variation between institutions proves that consensus does not exist. Consequently, patients benefit from a team-based approach wherein pulmonary physicians, interventional radiologists, and thoracic surgeons convene with each new patient to review all available clinical information and construct a collaborative approach akin to a tumor board. This approach has proven valuable for guiding diagnostic and therapeutic decisions for patients with idiopathic pulmonary fibrosis [29].

All experts agree with some fundamental principles of managing empyemas. Hospitalized patients with pneumonia should undergo evaluation to exclude clinically important volumes of pleural fluid. They also agree that parapneumonic effusions of sufficient size should be sampled by thoracentesis. But once evaluated by thoracentesis, a coordinated approach is necessary to determine algorithms of care. In order to validate the algorithms institutions might adopt, clinical outcomes should be closely monitored. Case series in the literature establish achievable outcomes in terms of duration of hospitalization and survival that should be achieved. If not achieved, local algorithms should be modified and reevaluated.

But for the future, continued status of empyema as a high-impact orphan disease strikes me as unacceptable. Our patients with pleural infections depend on us to have knowledge from robust and well-designed studies to guide their diagnosis and therapy. Learning from the success of advocates for COPD, we should encourage our funding agencies to recognize the public health impact of empyema and fund adequate research. It is time for empyema to relinquish its title as an orphan and regain its well-deserved status from the preantibiotic era as a harbinger of death. As busy clinicians, we need to advocate for more empyema research. Sir William Osler, who himself died of empyema, reminds us, ''At whose door so often lies the responsibility for death in cases of empyema but at that of the busy doctor ...'' [30]. He was speaking of busy physicians who fail to recognize the early signs of pleural infection and thereby delay therapy. We might now interpret his comments as an admonishment to encourage a more complete understanding of mechanisms of disease and management approaches.

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