

# Medical and Surgical Management of Empyema

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## Abstract

Infection of the pleural space is an ancient and common clinical problem, the incidence which is on the rise. Advances in therapy now present clinicians of varying disciplines with an array of therapeutic options ranging from thoracentesis and chest tube drainage (with or without intrapleural fibrinolytic therapies) to video-assisted thoracic surgery (VATS) or thoracotomy. A framework is provided to guide decision making, which involves weighing multiple factors (clinical history and presentation, imaging characteristics, comorbidities); multidisciplinary collaboration and active management are needed as the clinical course over a few days determines subsequent refinement. The initial choice of antibiotics depends on whether the empyema is community-acquired or nosocomial, and clinicians must recognize that culture results often do not reflect the full disease process. Antibiotics alone are rarely successful and can be justified only in specific circumstances. Early drainage with or without intrapleural fibrinolytics is usually required. This is successful in most patients; however, when surgical decortication is needed, clear benefit and low physiologic impact are more likely with early intervention, expeditious escalation of interventions, and care at a center experienced with VATS.

## Keywords

- ▶ empyema
- ▶ pleural infection
- ▶ tissue plasminogen activator
- ▶ deoxyribonuclease
- ▶ thoracoscopy
- ▶ video-assisted thoracic surgery

During World War I, the U.S. Army formed an empyema commission to address an epidemic of empyema among enlisted men in crowded camps and exacerbated by the 1918 influenza pandemic.<sup>1</sup> Their management recommendations were (1) early closed pleural drainage (through serial aspiration or closed chest tube), (2) avoidance of early open drainage, (3) sterilization and obliteration of the empyema cavity, and (4) maintenance of the patient's nutritional status.<sup>2</sup> One-hundred years later these remain core principles, despite major advances including antibiotic therapy, imaging techniques, intrapleural fibrinolytic drugs, and minimally invasive surgical techniques. Despite these advances, the morbidity, mortality, and burden of pleural infection remain high. Judging which interventions are needed to optimally manage an individual patient is complex and involves qualitative factors. While clinical studies provide guidance, ambiguity in how to apply the evidence remains.

This review aims to provide practical guidance to the general or respiratory physician or surgeon managing a patient

with pleural infection. We refer readers to other literature regarding topics not addressed here, such as the clinical and radiographic presentation of pleural infection,<sup>3</sup> management of postresection pleural space infection and empyema associated with a bronchial or esophageal fistula,<sup>4,5</sup> nonbacterial (mycobacterial, fungal) empyema, and pleural infection in children.<sup>6</sup>

## Incidence and Mortality of Pleural Infection

Parapneumonic effusion develops in 14 to 19% of patients with community-acquired pneumonia (CAP), and roughly a third of these patients will have empyema or complicated parapneumonic effusion (CPE).<sup>7,8</sup> However, the notion that empyema represents an extension of bacterial pneumonia is currently being challenged. Many patients with empyema lack imaging evidence of an underlying pneumonia; in a recent study, chest computed tomography (CT) demonstrated evidence of pneumonia in only 44% (64/164) of community-acquired empyema

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(CAE) cases and 27% (88/324) of health care associated empyema (HCAE).<sup>9</sup> Retrospective cohorts demonstrate no seasonal variation in empyema incidence, in contrast with the seasonality of pneumonia. The microbiology of CAP is remarkably different from that of CAE (see “Microbiology”). While occasionally pleural infection arises through hematogenous spread, from subdiaphragmatic infection, trauma, or iatrogenically from procedures, the mechanism for the development of many empyemas is unclear.

The crude and/or age-adjusted incidence of adult pleural infection is consistently rising in diverse cohorts and health systems (e.g., in Canada,<sup>10,11</sup> Denmark,<sup>12</sup> Finland,<sup>13</sup> and the United States).<sup>14,15</sup> The largest incidence ratio increase is in the elderly.<sup>11,12</sup> Because the 30-day/in-hospital case fatality rate of empyema (7–11%) has remained stable for over 30 years,<sup>14,15</sup> the rising incidence is not likely due to improved detection of clinically less-significant disease. This would be expected to dilute the case fatality rate, in fact one study found both an increasing incidence of empyema and incidence of empyema-specific deaths.<sup>16</sup>

Long-term outcomes of patients with pleural infection demonstrate high rates of readmission and repeated interventions. Among 4,095 patients with empyema, 21% were readmitted within 90 days and 27% of these readmissions were specifically secondary to the empyema.<sup>17</sup> Additionally, a subsequent procedure within 30 days was required in 51 and 39%, respectively, of patients managed initially with a chest tube or with initial surgery.<sup>17</sup> Although their baseline status is unclear, 22 to 31% of pleural infection patients are reportedly discharged to a facility instead of home.<sup>11,14</sup>

A substantial late mortality is reported after a pleural infection. The 1-, 3-, and 5-year mortality was 15, 24, and 30%, respectively, among 191 patients with empyema or CPE<sup>18</sup>; their 3-month mortality of 8% was similar to those of other prospective cohorts.<sup>19</sup> The majority (66%) of late mortality in patients with empyema is attributable to causes other than pneumonia or empyema.<sup>20</sup> Empyema often stems from underlying vulnerability—the high long-term mortality likely reflects these patients' substantial burden of comorbid disease.<sup>21</sup>

## General Principles of Management

### Timely Identification of Pleural Infection

An empyema is defined as pus in the pleural space or pleural fluid with organisms present on Gram stain or culture. CPE is defined as pleural fluid pH <7.20 or pleural fluid glucose <60 mg/dL with clinical evidence of infection. However, Gram-stain or culture-positive nonpurulent effusions are defined as “CPE” in some guidelines and reports and as “empyema” in others.

Empyema or CPE should be suspected in any patient with a pleural effusion and pneumonia or sepsis. Reliable demographic or clinical features that indicate empyema associated with CAP have not emerged.<sup>22</sup> Pleural infection is roughly twice as prevalent in men,<sup>11–13,15,23–25</sup> in patients with comorbidities (particularly diabetes mellitus,<sup>23,24,26–31</sup> hypoalbuminemia,<sup>7,8</sup> and alcoholism).<sup>7,8,26,32,33</sup> However, the only independent variable associated with empyema

( $n = 128$ ) among 1,080 patients with invasive pneumococcal infection was the pneumococcal serotype (not any clinical or demographic features).<sup>34</sup> Notably, pneumonia-specific and generic sepsis scores (such as the pneumonia severity index or CURB-65) on admission do not predict development of CPE or empyema.<sup>8</sup>

Because there are no clinical characteristics that identify an uncomplicated effusion in patients with pneumonia or sepsis, thoracentesis should be performed whenever such patients have >10 mm of pleural fluid.<sup>4,35,36</sup> A pleural effusion should be specifically sought for when patients with pneumonia fail to respond within 48 to 72 hours of antibiotic therapy, or in elderly patients (who often lack overtly infectious symptoms and present with dyspnea, anemia, or weight loss).<sup>37</sup>

Classification schemas for pleural infection differ regarding pleural fluid glucose thresholds (60<sup>38</sup> vs. 40 mg/dL<sup>35,39</sup>) and inclusion<sup>35,38</sup> or not<sup>39</sup> of pleural fluid lactate dehydrogenase measurement.<sup>40</sup> All classifications include pH measurement, but pH can be affected by residual air, heparin, or lidocaine in the sample,<sup>41</sup> can significantly vary between individual locules,<sup>42</sup> or be elevated by urease-producing organisms such as *Proteus*.<sup>43</sup> Therefore, a pleural effusion should not be classified and managed as uncomplicated solely by biochemical features; for borderline laboratory results the clinical context of the patient must be considered. Escalating therapy empirically or resampling the effusion is indicated whenever clinical questions linger.

### Timely Management of Pleural Infection

A three-stage classification of parapneumonic effusion (exudative, fibrinopurulent, and organizing) was proposed in 1962.<sup>44</sup> Early observations suggested that it took 2 to 3 weeks for the early exudate to become frankly purulent.<sup>2</sup> However, the time to progression from one stage to another is highly variable. Therefore, interventions should be performed expeditiously, and treatments escalated rapidly when the pleural process did not improve within a few days. There is no role for protracted “expectant” management of a potentially infected pleural space; delaying diagnostic thoracentesis of a parapneumonic effusion for an anticipated response to antibiotics alone is associated with increased hospital length of stay (LOS) and costs.<sup>45</sup> Similarly, delaying a chest tube >3 days after recognition of pleural fluid is associated with increased mortality.<sup>46</sup>

Preclinical models of pleural infection have demonstrated rapid progression of pleural organization within hours to days. In a *Pasteurella* rabbit model, less pleural rind was noted with chest tube placement 24 to 48 hours after pleural inoculation; with chest tube placement after 72 hours the pleura was similar to animals with no chest tube.<sup>47</sup> In this same model, pus and pleural fibrosis were consistently evident 96 hours after empyema induction.<sup>48</sup>

The time course of human pleural infection appears far more heterogeneous; the evidence generally supports that timely management is beneficial with the caveat that the absolute time interval is quite variable.<sup>45,46</sup> Surgical series (► **Table 1**) have generally focused on the rate of intraoperative conversion from video-assisted thoracic surgery (VATS) decortication to open thoracotomy. Delay is variably defined as time

**Table 1** Rates of conversion from initial VATS to thoracotomy in patients with empyema

1st author, year	Design	N	Prior therapy	Empyema stage	30-day mort. (%)	Conversion rate (%)	Factors associated with conversion	
							Not predictive	Predictive
Lawrence 1997 <sup>56</sup>	Retrospective	42	Failed med tmt	II–III	0	5, 29 <sup>a</sup>	Duration of symptoms Preop hospital stay	
Striffeler 1998 <sup>146</sup>	Retrospective	67 <sup>b</sup>	Failed med tmt	II	4	28	Chest CT features	None
Angelillo-Mackinlay 1999 <sup>147</sup>	Retrospective	53		II	2	6		
Cassina 1999 <sup>148</sup>	Prospective	45	Failed IPFT	II	0 <sup>c</sup>	18	Chest CT features	
Waller 2001 <sup>55</sup>	Prospective	36		II–III	6	42	Duration of symptoms Preop hospital stay	None
Waller 2001 <sup>50</sup>	Prospective	39		II	3	59		Preop hospital stay
Roberts 2003 <sup>149</sup>	Retrospective	172		II–III	2	62	CT pleural rind CT organized fluid	CT report “empyema”
Kim 2004 <sup>54</sup>	Retrospective	70	Failed med tmt	II–III	0	7	Duration of symptoms	
Lardinois 2005 <sup>51</sup>	Prospective	178	Chest tube 75%	II	3	44		Duration of symptoms Gram-neg organisms
Solaini 2007 <sup>150</sup>	Retrospective	110	Chest tube 65%	II–III	0	8		
Cardillo 2009 <sup>151</sup>	Retrospective	185	Failed med tmt	II–III	0	6		Stage III Duration of symptoms
Stefani 2013 <sup>52</sup>	Retrospective	97	Chest tube 61%	II–III	–	59	CRP Positive culture Loculated effusion	Duration of symptoms CT pleural rind Fever
Chung 2014 <sup>57</sup>	Retrospective	120 <sup>d</sup>	Chest tube 30%	II–III	0	1	Duration of symptoms	
Schweigert 2016 <sup>21</sup>	Retrospective	335		I, II, and III	9 <sup>c</sup>	13		
Jagelavicius 2017 <sup>53</sup>	Prospective	71		II–III	1	25	Chest CT features CRP, fever Positive culture	Duration of symptoms Frank pus
Reichert 2018 <sup>152</sup>	Retrospective	110		III	11	5		

Abbreviations: CT, computed tomography; neg, negative; IPFT, intrapleural fibrinolytic therapy; med tmt, medical treatment; Preop, preoperative.

Note: Empyema stage: I (exudative), II (fibrinopurulent), and III (organized).

<sup>a</sup>Intraoperative conversion in 2 of 42 cases (4.8%), 10 additional patients required open second procedure, so total open is 12/42 (29%).

<sup>b</sup>Symptom duration <3 wk; no visceral pleural thickening on CT.

<sup>c</sup>Duration not specified.

<sup>d</sup>16% had tuberculosis.

from hospital admission to operation<sup>49,50</sup> (precise but with many confounders) or as time from symptom onset to operation (more vague but potentially more reflective of the pathophysiology). The results of these analyses are conflicting and may also reflect the degree of experience with VATS decortication.

Multivariate analysis in several studies totaling 346 patients found that a longer duration of symptoms was associated with a higher rate of conversion from VATS to open thoracotomy (which occurred in 8–44% of cases).<sup>51–53</sup> The mean symptom duration in the successful VATS groups was 10 to 20 days compared with 17 to 30 days in the conversion groups.<sup>51,52</sup> The effect of symptom duration on conversion was continuous (i.e., there was no “inflection point” where management via VATS became difficult)<sup>51,53</sup>; each additional day of symptoms was associated with a greater odds ratio (OR) of conversion of 1.1 (1.0–1.2,  $p = 0.004$ ).<sup>53</sup>

However, others have reported low intraoperative conversion rates despite a long average duration of symptoms.<sup>54</sup> Two series found a similar mean duration of symptoms in VATS cases versus those requiring conversion (38 vs. 40 and

53 vs. 56 days).<sup>55,56</sup> Among 128 patients with surgically managed empyema, a longer symptom duration (<2, 2–4, and >4 weeks) was associated with a longer operative time (101, 125, and 139 minutes, respectively) and an increased rate of postoperative air leaks; however, there was no difference in the need for reoperation or additional drainage procedures and the rate of intraoperative conversion to thoracotomy was low throughout (only one patient with symptoms <2 weeks).<sup>57</sup> Overall, lower conversion rates in contemporary studies and from centers with more VATS cases suggest that the conversion rate is an unreliable surrogate for increasing organization of the pleural space as it is highly influenced by the surgeon and the setting.

There are little data regarding symptom duration and outcomes of intrapleural fibrinolytic therapy (IPFT). The favorable results of combined tissue plasminogen activator (tPA) and deoxyribonuclease (DNase) in the MIST2 trial (see “Intrapleural Fibrinolytic Therapy”) occurred in patients with a median symptom duration of 13 days.<sup>24</sup> Other retrospective series have reported good outcomes with a duration of symptoms of 9 to 13 days.<sup>58,59</sup> However, most studies of

IPFT include patients based on subjective physician judgment and omit mention of symptom duration.

### Should Frank Pus Be Managed Differently than Complicated Parapneumonic Effusion?

The distinction between frank pus and Gram-stain or culture-positive pleural fluid is somewhat arbitrary, and data are conflicting whether this influences outcomes. In unblinded surgical series, purulence is predictive of conversion from VATS to thoracotomy, reoperation, and perioperative mortality.<sup>49,53</sup> In one retrospective series, the *absence* of purulence predicted success using tube thoracostomy and streptokinase (positive predictive value [PPV] 93%), but the *presence* of purulence did not predict treatment failure (PPV 26%).<sup>60</sup> A planned subgroup analysis of two large randomized fibrinolytic trials (MIST1 and MIST2) did not demonstrate a difference in outcomes in purulent and nonpurulent patients.<sup>23,24</sup> Therefore, the presence of pus should not weigh heavily in choosing how to manage patients with empyema.

## Microbiology

### What Is the Microbiologic Yield in Pleural Infection?

The bacteriologic yield of empyema/CPE by routine pleural fluid culture is roughly 50%.<sup>24,25,61</sup> Frequently, blood cultures are the only positive culture results, so aerobic and anaerobic blood cultures should be obtained whenever pleural infection is suspected.<sup>62,63</sup> Culture positivity is consistently higher in nosocomial empyema or in intensive care unit patients (typically 72–85%).<sup>49,64–66</sup>

Several methods have been studied to increase the yield of pleural fluid culture. Inoculation of pleural fluid into blood culture bottles at the bedside (vs. submission to the laboratory in a sterile container) detects more organisms with low rates of contamination.<sup>31,63,67</sup> The use of polymerase chain reaction (PCR) of 16S ribosomal RNA (rRNA) improves the diagnostic yield (82 vs. 55% with conventional cultures)<sup>68</sup>; the bacteria identified solely by PCR are frequently anaerobes.<sup>69,70</sup> PCR technology can also be applied to tissue obtained from ultrasound-guided pleural biopsies, which increases the yield compared with conventional culture, again particularly for anaerobes.<sup>70</sup> However, the overall yield remains 55% despite combination testing (blood culture, pleural fluid culture, pleural fluid, and pleural biopsy 16S rRNA),<sup>70</sup> and PCR is not routinely available. Therefore, empiric antibiotics must often be guided by an understanding of the bacteria frequently encountered in specific settings.

### Bacteriology of Community-Acquired versus Healthcare-Acquired Empyema

The causative organisms are different if an empyema is community-acquired (CAE) or healthcare-acquired (HCAE). ▶ **Table 2** and ▶ **Fig. 1** summarize data from several studies of organisms isolated from the pleural fluid of nearly 1,500 patients (CAE, 825 and HCAE, 672).<sup>9,25,31,61,64,66,71,72</sup> In CAE, *Streptococcus* species account for roughly 50% of isolates, most commonly nonpneumococcal *Strep milleri*. Methicillin-resistant *Staph aureus* (MRSA) is uncommon, though case reports

**Table 2** Causative bacteria in community-acquired and hospital-acquired empyema

Organism isolates	Community-acquired empyema (n = 825)	Hospital-acquired empyema (n = 672)
Aerobic Gram-positives	745 (76%)	630 (65%)
<i>Streptococcus</i>	502 (51%)	169 (17%)
<i>Strep milleri</i> <sup>a</sup>	294 (30%)	136 (14%)
<i>Strep pneumoniae</i>	142 (14%)	11 (1%)
Other strep	66 (7%)	22 (2%)
<i>Enterococci</i>	23 (2%)	73 (8%)
<i>Staphylococcus</i> <sup>b</sup>	172 (18%)	310 (32%)
MSSA	84 (9%)	103 (11%)
MRSA	26 (3%)	84 (9%)
Other <i>Staph</i>	37 (4%)	89 (9%)
Other aerobes	48 (5%)	78 (8%)
Aerobic Gram-negatives	169 (17%)	325 (33%)
<i>E. coli</i>	27 (3%)	31 (3%)
<i>Klebsiella</i>	23 (2%)	42 (4%)
<i>Proteus</i>	7 (1%)	4 (0%)
<i>Enterobacter</i>	38 (4%)	75 (8%)
<i>Pseudomonas</i>	29 (3%)	70 (7%)
Other	45 (5%)	103 (11%)
Anaerobes	54 (6%)	19 (2%)
<i>Fusobacterium</i>	26 (3%)	3 (0%)
<i>Peptostreptococcus</i>	19 (2%)	2 (0%)
<i>Bacteroides</i>	20 (2%)	7 (1%)
<i>Prevotella</i>	16 (2%)	5 (1%)
Other	29 (3%)	15 (2%)
Other	17 (2%)	2 (0%)
Total isolates	985 (100%)	976 (100%)

Abbreviations: MRSA, methicillin-resistant *Staph aureus*; MSSA, methicillin-sensitive *Staph aureus*.

Note: Data are presented as number of isolates, n (%).

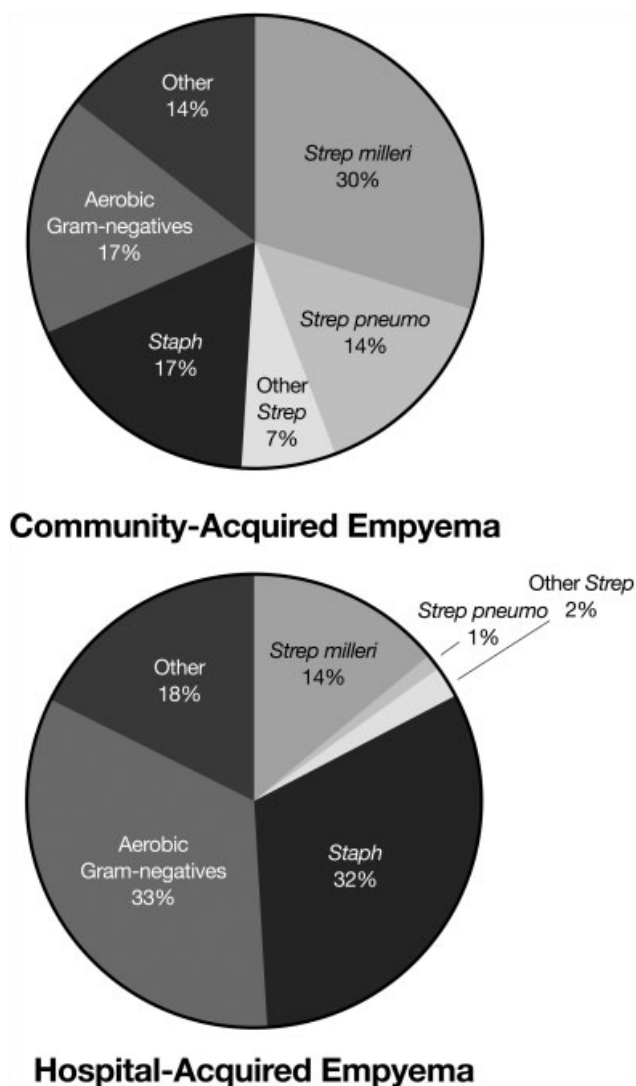
Data from <sup>9,25,31,61,64,66,71,72</sup>.

<sup>a</sup>Including *Strep viridians*.

<sup>b</sup>Meyer et al<sup>71</sup> did not describe *Staph aureus* resistance.

exist.<sup>73</sup> In HCAE, Gram-negative organisms are most common (particularly *Enterobacter*, *Pseudomonas*, and *Klebsiella*); Gram-positive isolates are primarily *Enterococci* and *Staph aureus*. MRSA appears to be fairly unique to HCAE, in some areas representing 25% of isolates.<sup>61</sup> In intensive care unit patients with HCAE, multidrug-resistant pathogens including extended spectrum  $\beta$ -lactamase (ESBL) producers and *Acinetobacter* must be considered.<sup>65</sup>

▶ **Table 2** suggests that anaerobes represent less than 5% of isolates, but this is a gross underestimation of their true prevalence. Anaerobic species (chiefly *Bacteroides*, *Fusobacterium*, and *Prevotella* spp.) are isolated in 74 to 76% of cases if rapid processing and fastidious culture techniques are



**Fig. 1** Causative bacteria from pleural infection in 825 patients with community-acquired infection (top) and 672 patients with hospital-acquired infection (bottom). Data from ▶ **Table 2**.

employed, or a reference anaerobic microbiology laboratory is used.<sup>74–77</sup> Furthermore, experimental evidence suggests potential synergy between anaerobes and *Strep milleri*.<sup>78</sup> The most compelling evidence for “occult” anaerobes in empyema/CPE fluid is detection of bacterial DNA or RNA using massive parallel sequencing. This approach identified anaerobic bacteria in 70% (19/27) patients with empyema and no known etiology (i.e., “primary” CAE), predominantly *Fusobacterium nucleatum*. By conventional culture only 37% of cases had growth, and the anaerobes were detected by culture in only 16% of the anaerobic cases.<sup>79</sup>

When anaerobes are present a longer duration of symptoms is often seen<sup>77,80</sup> or an atypical presentation, with vague chest pains, weight loss, and anemia—misleading one to suspect malignancy or tuberculosis.<sup>29,37,81</sup> Fever is also not universal in confirmed anaerobic pleural infection, as shown in one series where 40% of patients were afebrile and 40% had low-grade temperatures below 38.9°C.<sup>82</sup>

When *Strep pneumoniae* is isolated from pleural fluid, it is usually the only organism, even when advanced diagnostic

techniques are employed.<sup>61,68–70,79</sup> This may be because pneumococcus proliferates rapidly in exudative pleural fluid,<sup>83</sup> perhaps thereby excluding other bacteria.

### Does Culture Positivity or Specific Microbiology Identify High-Risk Patients?

Culture-positive pleural infection is associated with increased duration of drainage, failure of nonsurgical treatments, longer hospital LOS, complications, and death, compared with culture-negative cases.<sup>84,85</sup> Retrospective culture-positive cohorts display high in-hospital<sup>86</sup> as well as 1-year mortality (42–52% in some series).<sup>9,87</sup> However, culture positivity is consistently increased in HCAE and critically ill patients<sup>49,64–66</sup> and outcome differences are not borne out when the setting (HCAE vs. CAE) is taken into account.<sup>88</sup> Finally, culture positivity does not appear to predict success or failure of fibrinolytic therapy.<sup>89</sup>

In preclinical studies different bacteria may differentially affect pleural mesothelial cells<sup>90</sup> or upregulate fibrin deposition,<sup>91</sup> but clinical evidence does not demonstrate that specific bacteria are associated with worse outcomes. Although increased mortality with Gram-negative and *Staph* infections (irrespective of CAE or HCAE) was shown in one posthoc analysis of the bacteriology from a large, well-characterized randomized trial cohort,<sup>61</sup> subsequent (multivariate) analyses controlling for other factors showed that mortality is primarily dependent on patient factors and setting (CAE or HCAE) and not specific organisms.<sup>9,25,31,65,71</sup> Therefore, culture results should not influence the selection of interventions beyond the choice of antibiotics.

### Tube Thoracostomy

The optimal tube size to drain an empyema/CPE is controversial. The interventional radiology literature reports good outcomes with small ( $\leq 14$  Fr) catheters, but this may also reflect patient selection and precise image-guided tube placement.<sup>92,93</sup> Surgical series prefer large (32–40 Fr) tubes, with the rationale of reduced tube blockage by viscous fluid.<sup>62</sup> However, tube thoracostomy failure usually stems from persistent, loculated fluid and not direct tube obstruction.

A secondary analysis of the MIST1 trial provides some insight.<sup>94</sup> There was no difference in the surgical referral or mortality among groups with chest tubes of varying sizes (<10 Fr 36% [21/58]; 10–14 Fr 36% [75/208]; 15–20 Fr 40% [28/70]; >20 Fr 44% [30/69];  $p = 0.27$ ). Higher pain scores were reported with larger tubes during insertion and while the tube was in place.<sup>94</sup> However, the original trial left the choice of tube size with the treating physician, and there was a significant trend toward larger tubes in grossly purulent pleural fluid. Nevertheless, a planned analysis of the purulent subgroup did not demonstrate a disadvantage of smaller tubes.<sup>94</sup>

It appears that flushing of the tube is important, particularly with small tubes. In the MIST1 study, all tubes were flushed by protocol several times a day. Other series of small tubes (12 Fr) for nonpurulent CPE which were not routinely flushed found that obstruction occurred in 63% (61/97).<sup>95</sup> Therefore, we recommend initial insertion of a small-bore ( $\leq 14$  Fr) tube, but with routine flushing and monitoring for kinking.

## Intrapleural Fibrinolytic Therapy

### Background and Intrapleural Therapy Trials

Fibrin deposition can lead to pleural loculations and adhesions, inhibiting drainage and lung expansion. An appealing strategy is instillation of IPFT through a chest tube to effect enzymatic debridement. This could reduce the need for surgery, but might delay definitive therapy and increase costs and LOS. In the following sections, “IPFT” refers to the application of any fibrinolytic with or without DNase.

Earlier fibrinolytics, streptokinase and urokinase, have been studied in pleural infection in numerous placebo-controlled human trials with mixed results.<sup>96,97</sup> A more definitive answer was provided by the multicenter MIST1 study, involving 430 patients with empyema/CPE who received intrapleural streptokinase or placebo.<sup>23</sup> No difference was found in the rate of death or surgery at 3 months, hospital LOS, radiographic change, or lung function. These findings extended to subgroups of patients analyzed for the presence of loculations or purulent fluid.

The failure of streptokinase to demonstrate benefits over placebo in MIST1 led to the exploration of other agents and targets for enzymatic debridement. Empyema fluid contains extracellular DNA<sup>98</sup> which increases viscosity, and in animal models the addition of DNase to streptokinase<sup>99</sup> or tPA<sup>100</sup> improved liquefaction and drainage of empyema fluid. DNase may also disrupt bacterial biofilms<sup>101</sup> and reduce competition for binding to therapeutic fibrinolytics.<sup>102</sup>

This preclinical work, encouraging retrospective series,<sup>59,103–106</sup> as well as the failure of streptokinase in MIST1, prompted the study of intrapleural tPA, alone or in combination with DNase, in MIST2.<sup>24</sup> The interventions (tPA at a dose of 10 mg, DNase at a dose of 5 mg, or placebo) were given in four treatment arms: tPA + DNase, tPA + placebo, placebo + DNase, and placebo + placebo. The combination tPA + DNase arm had significantly reduced radiographic opacification (–30%) at 7 days (the primary outcome) compared with the other arms which were similar (tPA alone –17%, DNase alone –15%, placebo –17%). The combination arm also had significantly reduced surgical referral (OR: 0.17; 95% CI: 0.03–0.87) and significantly shorter hospital LOS (6.7 day reduction; CI: 12.0–1.9) compared with placebo. A reduction in surgical referral was also shown in a subsequent single-center randomized trial of 25 mg of tPA versus placebo in empyema or CPE, though only 6/68 patients included had a positive Gram-stain or frank pus, making generalization of these results difficult.<sup>107</sup> Recent cost analysis of the MIST2 cohort suggests that tPA + DNase is cost effective, though this should be confirmed in other health systems.<sup>108</sup>

Saline pleural irrigation may be a simple, cost-effective alternative to the MIST2 drugs. In a small ( $n = 35$ ), single-center pilot study, patients with pleural infection and incomplete drainage 24 hours after initial tube thoracostomy were randomized to three times daily irrigation with 250 mL of saline for 3 days versus drainage alone.<sup>109</sup> Using prespecified indications for surgical referral, the drainage alone group was more likely to require surgery (OR: 7.1; 95% CI: 1.23–41.0;

$p = 0.03$ ), reflecting a greater remaining effusion on repeat CT as compared with the saline group.

### Dosing of IPFT

The optimal dose, dwell time, dosing frequency, and duration of IPFT are not well defined. Individual doses of tPA range from 2 to 100 mg<sup>103,104</sup> and dwell times from 30 minutes<sup>105</sup> to 4 hours.<sup>110</sup> A prospective study (ADAPT) examined a tPA dose reduction to 5 mg.<sup>111</sup> Successful treatment (hospital discharge without needing surgery or mortality) occurred in 93% (57/61), though 5% experienced pleural bleeding requiring transfusion—similar to studies using higher doses. In this cohort patient selection and symptom duration were unclear, and 13% had indwelling pleural catheter-associated empyema, which is more likely to respond to antibiotics alone.<sup>112</sup> Therefore, we recommend fibrinolytic dosing from the MIST2 protocol with a tPA dose of 10 mg and DNase of 5 mg, as dose reductions of the tPA component offer no safety benefits and may not be universally effective.

Preclinical studies demonstrate that the inhibitor of fibrinolysis, plasminogen activator inhibitor-1 (PAI-1), largely accounts for the imbalance between fibrin deposition and fibrinolysis that favors septation and loculation in infected fluid.<sup>98,113,114</sup> PAI-1 irreversibly inactivates tPA in 1:1 fashion and human empyema PAI-1 levels are highly heterogeneous,<sup>98,115,116</sup> suggesting that IPFT dosing relative to measures of fibrin formation may be useful.<sup>117</sup> Phase I investigation of the fibrinolytic drug single-chain urokinase plasminogen activator (scuPA) that is relatively resistant to inhibition by PAI-1 is underway.<sup>118</sup>

In patients who failed to respond to the 3-day MIST2 regimen, an extended course of IPFT does not appear to be of benefit. A retrospective comparison of extended tPA and DNase (mean 9.8 doses, range 7–16) versus conventional (<6) doses found similar rates of needing surgery (15 vs. 16%), but nonsignificant trends toward more bleeding (10 vs. 3%), additional tube placement (35 vs. 15%), longer LOS (17 vs. 13 days), and greater need to escalate narcotics (80 vs. 57%).<sup>119</sup> Presumably extended dose patients were less fit for or refused surgery, but it appears that patients unsuccessfully drained after a short course of IPFT benefit more from additional image-guided tubes or surgery than prolonged IPFT dosing.

### Concurrent or Sequential?

In the MIST2 regimen, twice daily tPA and DNase were instilled sequentially, each allowed to dwell for 1 hour with at least 2 hours of drainage between drugs.<sup>24</sup> This is cumbersome, and simultaneous instillation of both drugs has been studied in a randomized control trial (RCT)<sup>120</sup> and retrospective series.<sup>30,121</sup> The RCT found no significant difference between concurrent (1-hour dwell) versus sequential administration in treatment success (75 vs. 78%), safety profile, and imaging (CT) improvement.<sup>120</sup> Retrospective series confirm excellent treatment success (85–90%) with concurrent administration with a 2-hour dwell time.<sup>30,121</sup> A large, multicenter retrospective study (RetroLysis) of the MIST2 regimen is underway and should provide “real world” dosing and efficacy information.

Delivery of tPA and DNase simultaneously appears reasonable, and if combined we would suggest administration twice daily with both drugs allowed to dwell for 2 hours. In a rabbit model of tetracycline-induced pleural injury, tPA continued to reduce loculations over 4 to 8 hours.<sup>122</sup> Two hours, however, has been used in prior studies and is a practical compromise between limiting the time the chest tube is clamped and maximizing effective fibrinolysis.

### Safety Profile of Intrapleural Fibrinolytic Therapy

Fibrinolytic enzymes have a high molecular weight (70 kDa for tPA) which limits systemic absorption from intrapleural administration.<sup>123</sup> Intrapleural streptokinase has little measurable effect on systemic fibrinolysis,<sup>124,125</sup> and intrapleural instillation of 25 mg of tPA has no effect on plasma coagulation profiles and fibrinogen levels.<sup>107</sup> However, several prospective studies (totaling 465 patients) using intrapleural tPA (5–10 mg) have reported pleural bleeding in 0 to 5% of cases.<sup>24,111,120,126,127</sup> The bleeding was managed conservatively in all (transfusion and cessation of IPFT); no patients experienced systemic bleeding. The safety profile of tPA at doses higher than 5 to 10 mg is somewhat conflicting and limited to smaller patient samples. Two small studies suggested an increased risk of intrapleural bleeding at tPA doses of 20 to 25 mg (including intrapleural bleeding requiring operative exploration).<sup>106,128</sup> However, a randomized crossover trial of 25 mg of tPA versus placebo found a 3% rate of intrapleural bleeding.<sup>107</sup> Other retrospective studies suggest that intrapleural bleeding may be idiosyncratic and independent of the tPA dose.<sup>103,104</sup> These reports used various doses (commonly 50 mg and up to 100 mg), and only two of 161 patients experienced bleeding at the chest tube site with no intrapleural or systemic bleeds.

A small, single-center retrospective series of intrapleural tPA in anticoagulated or thrombocytopenic patients suggested a safety profile comparable to the cohorts above.<sup>129</sup> While the risk of systemic bleeding appears to be low, withholding anticoagulation while undergoing IPFT is reasonable if the indication for anticoagulation allows. Should intrapleural bleeding occur, supportive care is generally sufficient.

### Medical Thoracoscopy

Medical thoracoscopy (or pleuroscopy) is typically performed under moderate sedation by a pulmonologist using a single access port and rigid or semirigid instruments. It allows visual inspection, drainage, pleurodesis procedures, and directed parietal pleural biopsy. VATS is usually performed under general anesthesia with single lung ventilation by a surgeon, often with several entry ports and rigid instruments, and allows a full range of thoracic surgical procedures including decortication.

Series of medical thoracoscopy in empyema report success rates (no further interventions required) of between 75 and 91%,<sup>85,130,131</sup> with better results in free-flowing compared with organized empyema. However, in one series, thoracoscopy was performed after an average of 6 days of

tube drainage and 18 days from symptom onset.<sup>131</sup> Medical thoracoscopy can disrupt pleural adhesions but not achieve lung re-expansion when there is a visceral rind, and has limited ability to control bleeding. Clinical trials are ongoing comparing medical thoracoscopy with intrapleural fibrinolysis (NCT02973139 and NCT03468933).

## Surgical Therapy

### Medical versus Surgical Therapy

Two randomized trials compared immediate VATS to tube thoracostomy ( $\pm$ IPFT) for empyema/CPE.<sup>132,133</sup> The first found fewer treatment failures (using prespecified criteria), shorter duration of chest tubes and hospitalization in the surgical arm, but involved only a total of 20 patients.<sup>132</sup> The other RCT ( $n = 70$ ) involved only VATS debridement, but found that immediate VATS was associated with a shorter LOS (8 vs. 13 days) and less need for open decortication (17 vs. 37%,  $p < 0.05$ ).<sup>133</sup> However, this trial was unblinded and lacked prespecified criteria for surgical intervention in the medical arm, which occurred more frequently (37%) than in the placebo arms of MIST1/MIST2 (14–16%).<sup>23,24</sup> Neither study allows conclusions comparing surgery to more effective IPFT regimens with tPA and DNase, and until additional clinical trials (NCT03584113, NCT03583931, and NCT02165891) comparing early VATS to IPFT result, there are no robust data to say that one management strategy is superior.

### Which Surgical Approach Is Needed?

Drainage and IPFT with tPA and DNase can fail in approximately 30% of patients, who will require surgery if they are candidates.<sup>89,120</sup> Interpretation of mortality data in surgical cohorts is hindered by patient selection, as population-based studies of empyema report 30-day mortality rates of 11%<sup>14,17</sup> whereas many single institutions that primarily performed VATS decortication report 30-day mortality rates of 0% (**Table 1**). Overall, surgically managed patients are younger, less acutely ill, and have fewer comorbidities than those managed nonoperatively; in-hospital mortality in nonoperated patients with empyema/CPE is 15% compared with 5 to 6% in patients managed with surgery.<sup>14</sup>

The rate of conversion from a VATS to open decortication in **Table 1** is quite variable. It is not clear why—specifically stage of the empyema, symptom duration, study size, publication date, and prior treatment (though infrequently described) do not clearly correlate. Furthermore, attempts to identify factors predictive of conversion within a study are variable—for every study identifying a factor there is another finding no impact. Thoracic surgery generally has transformed from primarily open thoracotomy to primarily VATS approaches, but at varying rates and extent in different centers—this degree of heterogeneous experience with VATS is likely also a factor in single-center/single-operator reports. If available, there is little to be lost by initial VATS exploration in all cases other than a negligible increase in operative time associated with the thoracotomy conversion.<sup>52,55</sup>

## Practical Framework for Management

Many algorithms have been proposed that approach the management of pleural infection as a series of binary choices.<sup>3,35,134–137</sup> However, actual clinical decision making for individual patients involves simultaneously integrating multiple variables, including patient-related, pleural space characteristics, and availability of expertise and resources. Additionally, management of these patients is best conceptualized as a process, as the treatment response and the course of the illness strongly influence ongoing management.

We recommend active management with multidisciplinary communication between dedicated chest physicians, interventional pulmonologists, and general or thoracic surgeons who share experience in the treatment of pleural infection. It is intuitive that this is beneficial given the complexity of the decision making and the number of factors and interventions involved—however, the impact of such collaboration has not been studied.

## Antibiotic Management

Appropriate antibiotic selection for empyema/CPE is associated with improved survival in multivariate analyses.<sup>71,86</sup> When available, culture results are informative, but empiric treatment for HCAE or CAE is needed initially and for (frequent) culture-negative cases. For HCAE, coverage should include anaerobes, MRSA, as well as *Pseudomonas* (e.g., vancomycin, cefepime, and metronidazole, OR vancomycin and piperacillin/tazobactam dosed for activity against *Pseudomonas*).

For CAE, coverage should include penicillin-resistant *Streptococcus* and methicillin-sensitive *Staph aureus* (MSSA). Anaerobic coverage should be the rule, generally even when a

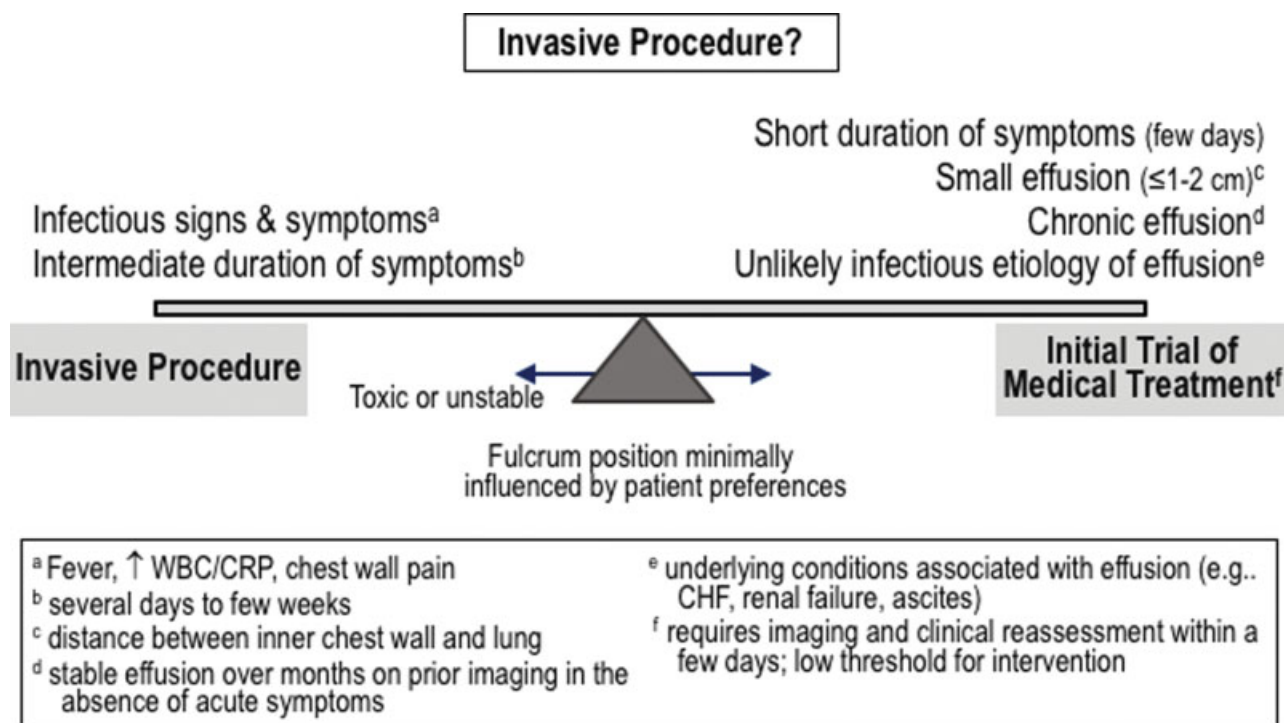
single aerobic pathogen is isolated, because of frequent (~75%) coexisting anaerobes—e.g., metronidazole, a  $\beta$ -lactam plus  $\beta$ -lactamase inhibitor (amoxicillin-clavulanate, ampicillin-sulbactam, piperacillin-tazobactam), or a carbapenem. If clindamycin is used local resistance patterns should guide coverage for resistant *Bacteroides fragilis*. Anaerobic coverage can be omitted only with proven pneumococcal infection (as recommended in the British Thoracic Society Guideline).<sup>35</sup> Addition of a macrolide to cover atypical CAP pathogens (*Mycoplasma* and *Legionella*, for example) in empyema is unnecessary.<sup>61</sup> Empyema due to *Legionella* is exceptionally rare and associated with small volume effusions.<sup>7,138,139</sup>

The appropriate duration of antimicrobial therapy is unclear. A small study found a trend toward fewer failures with longer courses of parenteral, but not oral, therapy.<sup>26</sup> Typically, parenteral therapy is continued until objective clinical and biochemical improvement occurs (including adequate pleural drainage)—then changed to oral therapy. The total duration of therapy is generally 3 to 6 weeks, depending on the patient's clinical response.

## When Can an Initial Trial of Antibiotics Alone Be Justified?

“The sun should never set on a parapneumonic effusion.”<sup>140</sup>

There are only a few specific scenarios in which a trial of treatment without an invasive procedure is justified in a patient with signs and symptoms of infection and a pleural effusion (→ Fig. 2). Although it is widely believed that stage I (exudative) effusions resolve with antibiotics alone (without drainage),<sup>35,39</sup> unsuccessful outpatient management with



**Fig. 2** Schematic balance of factors for or against trial of antibiotics alone without drainage. There are few specific scenarios in which a trial of treatment without an invasive procedure is justified (see the text for details). CHF, congestive heart failure; CRP, C-reactive protein; WBC, white blood cell.



antibiotics alone is reported in 28 to 67% of patients with empyema/CPE.<sup>71,72</sup> If management with antibiotics alone is attempted in very small (i.e., 1–2 cm) effusions, frequent monitoring (including imaging) every few days is needed. The transition from thin fluid to a densely organized process is variable but often occurs within days, and postponing an invasive procedure to directly address the empyema/CPE is clearly associated with prolonged hospital LOS and costs. Delaying interventions is associated with progressively complicated surgical management (e.g., conversion, operative time) which may be partially mitigated by more advanced VATS experience. The general impression is that early drainage is more successful, but the optimal drainage method has not been well studied.

Patient preferences have little impact regarding whether to directly address the pleural process outside of a comfort measures only setting. It is not a question of whether one prefers an invasive procedure or not—the question is whether to do it early or do it later, with associated prolonged hospitalization and increased likelihood of requiring a procedure with greater invasiveness. The risk of thoracentesis or tube placement per se is minimal, even in ICU patients. Too often these relatively minor interventions are deferred due to acuity of illness, comorbidities, or age, when in fact these patients should be managed aggressively as they are the least able to undergo treatment escalation later on.

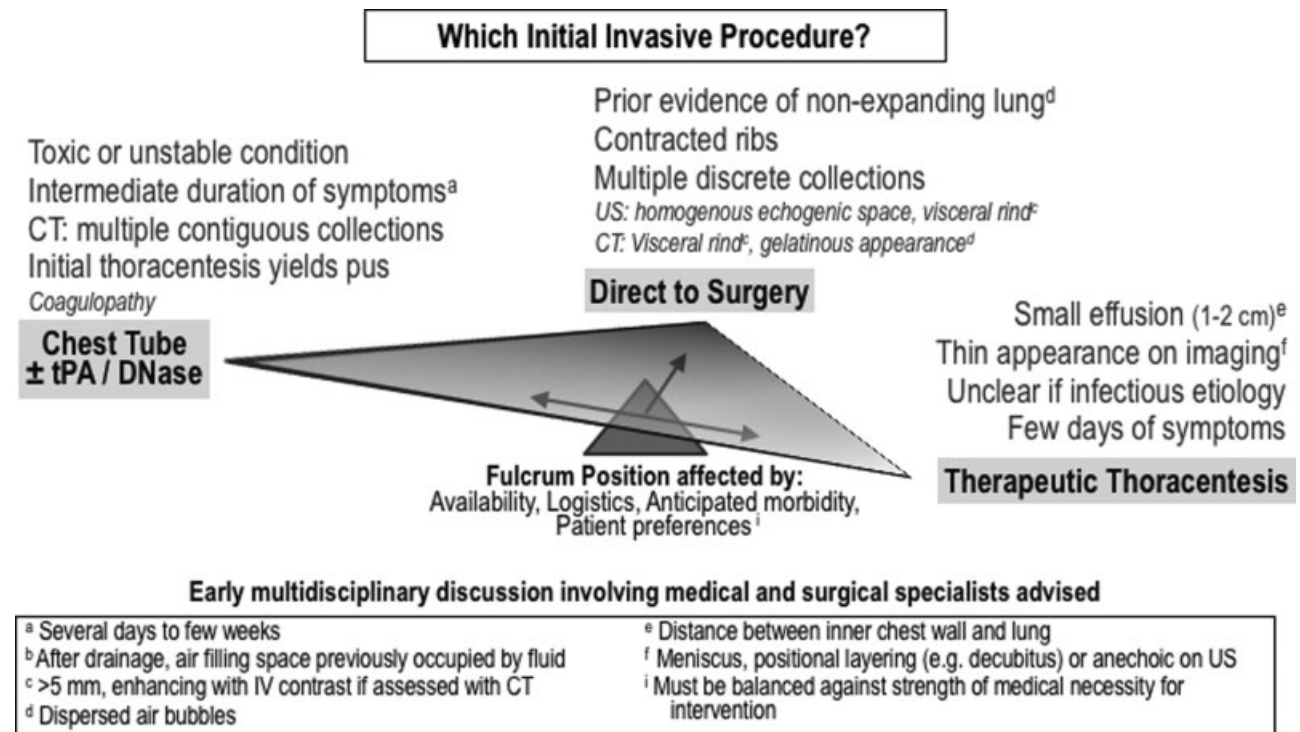
**Choice of Initial Procedure**

Selection of the appropriate invasive procedure involves a multifaceted balance of factors (→Fig. 3). Factors in italics

have weaker impact (i.e., less consistently predictive of outcome, or subjective). Accurate symptom duration should be sought; prior imaging even if done only a few days earlier can be very helpful.

It is rare that at least a diagnostic thoracentesis is not needed. Aspiration of cloudy fluid and especially frank pus during thoracentesis indicates the need for at least an indwelling tube but has less predictive power beyond that. The more ill the patient is, the greater the imperative that source of the illness must be fully addressed, so it is generally best to proceed with thoracostomy placement rather than thoracentesis alone. Similarly, in patients with coagulopathy an indwelling tube allows assessment and evacuation of any potential pleural bleeding.

Few patients can be predicted a priori to need surgical intervention. While sonographic (e.g., internal septae, echogenicity) or CT features (e.g., loculations, pleural rind) can suggest that thoracentesis alone is likely insufficient, these features are more variable in predicting whether drainage alone, IPFT, or surgical decortication will be needed.<sup>93,141,142</sup> Administrative database studies suggest potential overuse of proceeding directly to surgery, perhaps reflective of delayed involvement of clinicians knowledgeable about empyema/CPE and inexperience with IPFT. However, it is occasionally evident that drainage and IPFT will be suboptimal (multiple separate loculations or extensive fibrosis with contracted ribs and a thick fibrotic rind). If the likelihood is low that drainage and IPFT will be successful, it may be reasonable in good surgical candidates to go directly to surgery. Advanced age alone should not preclude surgical management.<sup>143</sup>



**Fig. 3** Approach to the initial procedure selection in a patient with suspected pleural infection (i.e., pleural effusion accompanied by sepsis or pneumonia). The factors favoring each procedure (therapeutic thoracentesis, chest tube, or direct surgery) are denoted, with italics indicating minor factors which the authors consider to be more equivocal. See the text for further explanation. DNase, deoxyribonuclease; tPA, tissue plasminogen activator.

If VATS inspection surprisingly reveals a less organized pleural space that might have responded to drainage and IPFT, little morbidity has occurred and the approach may have nonetheless contributed to a shorter LOS.

### Subsequent Procedure(s)

An early, appropriately chosen initial invasive procedure is sometimes only partially successful. Patients must be followed clinically and with imaging; it is generally clear within 1 to 2 days if further intervention is needed. It is intuitive that proceeding to next steps expeditiously would shorten the duration of the illness, but this has not been studied. Nevertheless, we suggest that rarely is more than 1 day useful to assess whether tube drainage or IPFT has been successful, and active assessment by physicians experienced in empyema/CPE is critical. The patient's clinical condition (fever, white blood cell or C-reactive protein, chest pain, appetite, signs of sepsis) is also an important factor.

High-quality evidence from the MIST2 RCT suggests that tPA + DNase is successful in most patients who fail drainage alone. Although ambiguity remains regarding patient selection, this suggests that at least a brief trial of IPFT is worthwhile in properly selected patients. For simplicity we suggest concurrent instillation of 10 mg tPA and 5 mg DNase with a dwell time of 2 hours (though data defining this as optimal are soft).

Treatment is not needed if pleural thickening or small sterile fluid cavities remain in patients whose clinical signs and symptoms of infection have resolved. Such residual pleural findings often resolve on long-term follow-up.<sup>144,145</sup>

### Conclusion

The challenge in management of thoracic empyema lies in the fact that the “outcome” of the empyema in a given patient represents the interaction of three highly variable domains: host/pathogen factors (patient comorbid diseases, physiologic reserves, and host immune responses), pleural space factors (the degree of macroscopic organization and loculation, pleural fluid biochemistry, and fibrinolytic inhibitor levels), and therapeutic interventions (antimicrobials, drainage, IPFT, surgery, and the timeliness of therapy or lack thereof). The independent contributions of patient and pleural space factors to the outcome, as well as the degree to which they are modifiable by interventions, remain in many cases undefined, and there is no one key factor or treatment decision that consistently will predict outcomes in most patients. Although empyema has been described since the time of Hippocrates, much practice remains based on historical convention. It is only through improved early risk stratification, patient selection, and personalization of therapies that clinicians will be able to fundamentally alter the course of this common and highly morbid clinical problem.

#### Disclosure Statement

The authors have no relationship with a commercial company that has a direct financial interest in subject matter or materials discussed in the article or with a company making a competing product.

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