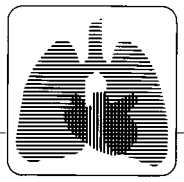

aacp consensus statement

Medical and Surgical Treatment of Parapneumonic Effusions*

An Evidence-Based Guideline

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Objective: **A panel was convened by the Health and Science Policy Committee of the American College of Chest Physicians to develop a clinical practice guideline on the medical and surgical treatment of parapneumonic effusions (PPE) using evidence-based methods.**

Options and outcomes considered: **Based on consensus of clinical opinion, the expert panel developed an annotated table for evaluating the risk for poor outcome in patients with PPE. Estimates of the risk for poor outcome were based on the clinical judgment that, without adequate drainage of the pleural space, the patient with PPE would be likely to have any or all of the following: prolonged hospitalization, prolonged evidence of systemic toxicity, increased morbidity from any drainage procedure, increased risk for residual ventilatory impairment, increased risk for local spread of the inflammatory reaction, and increased mortality. Three variables, pleural space anatomy, pleural fluid bacteriology, and pleural fluid chemistry, were used in this annotated table to categorize patients into four separate risk levels for poor outcome: categories 1 (very low risk), 2 (low risk), 3 (moderate risk), and 4 (high risk). The panel's consensus opinion supported drainage for patients with moderate (category 3) or high (category 4) risk for a poor outcome, but not for patients with very low (category 1) or low (category 2) risk for a poor outcome.**

The medical literature was reviewed to evaluate the effectiveness of medical and surgical management approaches for patients with PPE at moderate or high risk for poor outcome. The panel grouped PPE management approaches into six categories: no drainage performed, therapeutic thoracentesis, tube thoracostomy, fibrinolytics, video-assisted thoracoscopic surgery (VATS), and surgery (including thoracotomy with or without decortication and rib resection). The fibrinolytic approach required tube thoracostomy for administration of drug, and VATS included postprocedure tube thoracostomy. Surgery may have included concomitant lung resection and always included postoperative tube thoracostomy. All management approaches included appropriate treatment of the underlying pneumonia, including systemic antibiotics.

Criteria for including articles in the panel review were adequate data provided for ≥ 20 adult patients with PPE to allow evaluation of at least one relevant outcome (death or need for a second intervention to manage the PPE); reasonable assurance provided that drainage was clinically appropriate (patients receiving drainage were either category 3 or category 4) and drainage procedure was adequately described; and original data were presented. The strength of panel recommendations on management of PPE was based on the following approach: level A, randomized, controlled trials with consistent results or individual randomized, controlled trial with narrow confidence interval (CI); level B, controlled cohort and case control series; level C, historically controlled series and case series; and level D, expert opinion without explicit critical appraisal or based on physiology, bench research, or "first principles."

Evidence: **The literature review revealed 24 articles eligible for full review by the panel, 19 of which dealt with the primary management approach to PPE and 5 with a rescue approach after a previous approach had failed. Of the 19 involving the primary management approach to PPE, there were 3 randomized, controlled trials, 2 historically controlled series, and 14 case series. The number of patients included in the randomized controlled trials was small; methodologic weaknesses were found in the 19 articles describing the results of primary management approaches to PPE.**

The proportion and 95% CI of patients suffering each of the two relevant outcomes (death and need for a second intervention to manage the PPE) were calculated for the pooled data for each management approach from the 19 articles on the primary management approach. The pooled proportion of deaths was higher for the no drainage (6.6%), therapeutic thoracentesis (10.3%), and tube thoracostomy management approaches (8.8%) than for the fibrinolytic (4.3%), VATS (4.8%), and surgery (1.9%) approaches, but the 95% CI showed considerable overlap among all six possible primary management approaches. The pooled proportion of patients needing a second intervention to manage the PPE was also higher for the no drainage (49.2%), therapeutic thoracentesis (46.3%), and tube thoracostomy (40.3%) management approaches than the fibrinolytic (14.9%), VATS (0%), and surgery (10.7%) approaches; there was no overlap in the 95% CI between the first three and the last three management approaches, indicating a nonrandom difference.

Recommendations: **The studies identified through a careful literature review as relevant to the medical and surgical management of PPE have significant methodological limitations. Despite these limitations in the data, there did appear to be consistent and possibly clinically meaningful trends for the pooled data and the results of the randomized, controlled trials and the historically controlled series on the primary management approach to PPE. Based on these trends and consensus opinion, the panel recommends the following approach to managing PPE:**

• In all patients with acute bacterial pneumonia, the presence of a PPE should be considered. Recommendation based on level C evidence.

• In patients with PPE, the estimated risk for poor outcome, using the panel recommended approach based on pleural space anatomy, pleural fluid bacteriology, and pleural fluid chemistry, should be the basis for determining whether the PPE should be drained. Recommendation based on level D evidence.

• Patients with category 1 or category 2 risk for poor outcome with PPE may not require drainage. Recommendation based on level D evidence.

• Drainage is recommended for management of category 3 or 4 PPE based on pooled data for mortality and the need for second interventions with the no drainage approach. Recommendation based on level C evidence.

• Based on the pooled data for mortality and the need for second interventions, therapeutic thoracentesis or tube thoracostomy alone appear to be insufficient treatment for managing most patients with category 3 or 4 PPE. Recommendation based on level C evidence. However, the panel recognizes that in the individual patient, therapeutic thoracentesis or tube thoracostomy, as planned interim steps before a subsequent drainage procedure, may result in complete resolution of the PPE. Careful evaluation of the patient for several hours is essential in these cases. If resolution occurs, no further intervention is necessary. Recommendation based on level D evidence.

• Fibrinolytics, VATS, and surgery are acceptable approaches for managing patients with category 3 and category 4 PPE based on cumulative data across all studies that indicate that these interventions are associated with the lowest mortality and need for second interventions. Recommendation based on level C evidence.

(CHEST 2000, 18:1158–1171)

Key words: empyema; fibrinolytics; parapneumonic effusion; thoracentesis

Abbreviations: ACCP = American College of Chest Physicians; CI = confidence interval; HSP = Health and Science Policy Committee; PPE = parapneumonic effusion; VATS = video-assisted thoracoscopic surgery

Parapneumonic effusions (PPE) develop in up to 57% of patients hospitalized with bacterial pneumonia.[1–3] Some of these PPE will resolve without specific therapy other than antibiotic treatment of the underlying pneumonia. Other PPE must be drained for the patient to recover. Clinical approaches to choosing which PPE should be drained and the appropriate method(s) for draining these PPE vary.[3,4] The Health and Sciences Policy Committee (HSP) of the American College of Chest Physicians (ACCP) recognized this variability in clinical practice and convened a panel of experts in this field to develop a clinical practice guideline on the medical and surgical treatment of PPE. This document presents the evidence-based recommendations of this panel.

Materials and Methods

Choice of Topic, Panel, and Objectives

The HSP is charged by the ACCP Board of Regents to make recommendations on issues of clinical policy and to oversee preparation of clinical practice guidelines. The HSP solicits nominations for topics for clinical practice guidelines through an annual survey of the ACCP membership. Criteria for selecting nominated topics are: topics that are controversial or have conflicting data; topics that have wide variability in practice; conditions in which diagnosis and management of disease could be significantly improved by change in practices; topics that relate to multiple disciplines represented by the ACCP; and topics that have adequate published data to support a clinical practice guideline. The topic "Medical-Surgical Treatment of Parapneumonic Effusions" was nominated in the 1995 survey. The HSP identified this topic as meeting these criteria and chose it for development of a clinical practice guideline in 1996.

The HSP selected a panel composed of a chair (chosen as a facilitator and organizer), expert representatives from relevant liaison organizations (in addition to the ACCP, these included the American Thoracic Society, American College of Radiology, American Association of Thoracic Surgeons, and the Infectious Disease Society of America), and consultant methodologists. In addition to numerous teleconferences among small groups, the full panel met on two separate occasions. On April 29, 1997, the panel met to agree on the objectives, audience, scope, and general methods for the clinical practice guideline. On March 23, 1998, the panel met to agree on an approach for evaluating the risk categorization for PPE and to review the specific tasks required to make evidence-based recommendations about the medical and surgical treatment of PPE.

The panel's primary objective was to develop a clinical practice guideline on the evaluation and management of PPE using evidence-based methods.[5–7] The diagnosis of acute bacterial pneumonia was assumed to be established by appropriate clinical criteria. (The treatment of acute bacterial pneumonia is outside the scope of this guideline.) Specifically excluded from consideration were pleural effusions complicating trauma, postoperative pleural effusions, preexisting pleural effusions, and chylous pleural effusions. Secondary objectives were to enhance communication within the medical community about PPE by standardizing categorization of this problem, to encourage clinical research in this field by defining areas of uncertainty, to improve the quality of clinical research on PPE by pointing out the lack of rigorous controlled trials in this field, and to improve outcome for patients with PPE by providing a rigorous assessment of the clinical research supporting the various available management options. This clinical practice guideline is intended for all physicians caring for adults with pneumonia.

Evaluating PPEs

To evaluate PPE, the panel recommends categorizing patients with PPE by their risk for a poor outcome. Establishing a method of risk categorization was critical because management options would be based on the estimated risk for poor outcome. Estimates of the risk for poor outcome were based on the clinical judgment that, without adequate drainage of the pleural space, the patient with PPE would be likely to have any or all of the following: prolonged hospitalization, prolonged evidence of systemic toxicity, increased morbidity from any drainage procedure, increased risk for residual ventilatory impairment, increased risk for local spread of the inflammatory reaction, and increased mortality. The panel recognizes that further clinical research is needed to better quantify the risks for poor outcome by the categorization scheme proposed.

Based on consensus of clinical opinion, the expert panel developed an annotated table (Table 1) for evaluating the risk for poor outcome in patients with PPE based on three variables, pleural space anatomy, pleural fluid bacteriology, and pleural fluid chemistry. The individual features of each of the three variables used to distinguish risk categories were supported by appropriate literature sources.[8–15] This annotated table groups patients into four separate categories of risk for poor outcome. Insufficient data were available to reach consensus on how various patient characteristics, *eg*, age, comorbid disease, and evidence of persistent inflammatory response despite appropriate antibiotic therapy, might affect these risk categories. The panel's consensus opinion supported drainage for patients with moderate (category 3) or high (category 4) risk for a poor outcome, but not for patients with very low (category 1) or low (category 2) risk for a poor outcome.

Identifying Literature on Management Options for PPE

A literature review was performed for all medical and surgical treatments of PPE identified by panel members as clinically appropriate. MEDLINE was searched from 1966 through April 1, 1998, using the key terms pleural effusion, parapneumonic effusion, and empyema, each linked to thoracoscopy, thoracentesis, thoracostomy, chest tube, fibrinolytic agents, thrombolytic

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Table 1—*Categorizing Risk for Poor Outcome in Patients With PPE*

Pleural Space Anatomy		Pleural Fluid Bacteriology		Pleural Fluid Chemistry*	Category	Risk of Poor Outcome	Drainage
A_0 minimal, free-flowing effusion (< 10 mm on lateral decubitus)†	AND	B_X culture and Gram stain results unknown	AND	C_X pH unknown	1	Very low	No‡
A_1 small to moderate free-flowing effusion (> 10 mm and < ½ hemithorax)	AND	B_0 negative culture and Gram stain§	AND	C_0 pH ≥ 7.20	2	Low	No‖
A_2 large, free-flowing effusion (≥ ½ hemithorax)¶ loculated effusion,# or effusion with thickened parietal pleura**	OR	B_1 positive culture or Gram stain	OR	C_1 pH < 7.20	3	Moderate	Yes
		B_2 pus			4	High	Yes

*pH is the preferred pleural fluid chemistry test,[8] and pH must be determined using a blood gas analyzer.[9,10] If a blood gas analyzer is not available, pleural fluid glucose[8] should be used (P_0 glucose ≥ 60 mg/dL; P_1 glucose < 60 mg/dL). The panel cautions that the clinical utility and decision thresholds for pH and glucose have not been well-established.

†Clinical experience indicates that effusions of this size do not require thoracentesis for evaluation, but will resolve.[2]

‡If thoracentesis were performed in a patient with A_0 category pleural anatomy and P_1 or B_1 status found, clinical experience suggests that the P_1 or B_1 findings might be a false-positive. Repeat thoracentesis should be considered if effusion enlarges and/or clinical condition deteriorates.

§Regardless of prior use of antibiotics.

‖If clinical condition deteriorates, repeat thoracentesis and drainage should be considered.

¶Larger effusions are more resistant to effective drainage, possibly because of the increased likelihood that large effusions will also be loculated.[11]

#Pleural loculations suggest a worse prognosis.[12]

**Thickened parietal pleura on contrast-enhanced CT suggests presence of empyema.[13–15]

therapy, streptokinase, urokinase, x-ray CT, ultrasonography, drainage, rib resection, and thoracotomy. Articles were restricted to English language and human studies. The reference lists of MEDLINE-retrieved articles were reviewed for titles of other, possibly relevant, articles. In addition, each panel member identified relevant articles in their own personal files for possible eligibility. Abstracts of articles obtained through this search were reviewed to determine eligibility for full panel review. If the abstract provided insufficient information, the full journal article was obtained and reviewed for eligibility. Criteria for including an article in the full panel review were as follows:

1. Adequate data were provided for ≥ 20 adult patients with PPE to allow evaluation of at least one relevant outcome (death or need for a second intervention to manage the PPE).
2. Reasonable assurance was provided that drainage was clinically appropriate (patients receiving drainage were in either categories 3 or 4 based on the risk approach developed by the panel) and drainage procedure was adequately described.
3. Original data were presented (*ie*, data from patients reported multiple times in the literature by the same authors were only recorded once, and reviews were not acceptable).

Analysis of Management Options for PPE

Separate data abstraction forms for case series and historically controlled series and for randomized, controlled trials were developed, pilot tested, and refined. Information about study design (including quality assessments), study setting, patient characteristics, diagnostic testing, treatments, and outcomes were recorded on these abstraction forms. Abstraction forms were completed by at least two panel members for each journal article included for full review. After completion of the data abstraction forms by each individual reviewer, inconsistencies in data entry among reviewers were reconciled by the methodologists, and one final data abstraction form was submitted for each article. Data from the final forms were used to create the evidence tables.

The panel grouped PPE management approaches into six categories: no drainage performed, therapeutic thoracentesis, tube thoracostomy, fibrinolytics, video-assisted thoracoscopic surgery (VATS), and surgery (including thoracotomy with or without decortication and rib resection). The fibrinolytic approach required tube thoracostomy for administration of drug, and VATS included postprocedure tube thoracostomy. Surgery may have included concomitant lung resection and always included postoperative tube thoracostomy. All management approaches included appropriate treatment of the underlying pneumonia, including systemic antibiotics. The PPE management approaches were distinguished as either primary or rescue. Primary were those performed as the first approach to managing the PPE and rescue were those performed only after an earlier approach had failed.

Within each article, cohorts were defined, first, by whether drainage was clinically appropriate according to the panel's risk estimation method (category 3 and 4) and, second, by the PPE management approach. Data on two relevant outcomes, death and the need for a second intervention to manage the PPE, were used in this analysis. In most of the studies reviewed, a causal relationship between the PPE and death could not be determined; consequently, only total deaths, not attributable deaths, were considered. The denominator used to calculate the proportion of patients requiring a second intervention to manage the PPE was not corrected for deaths, because most clinical circumstances should allow a second intervention to manage the PPE before death. The proportion and 95% confidence interval (CI) of patients either dying or requiring a second intervention to manage the PPE were calculated by management approach for each cohort within a study. The proportion and 95% CI of patients suffering each of the two relevant outcomes were then calculated for the pooled data of individual cohorts for each management approach. Formal tests for heterogeneity of the data pooled across all studies within each management approach were not performed because review of the proportions showed wide variability. Data from studies reporting primary and rescue management approaches to PPE are presented separately.

Consensus on recommendations was reached after review of the evidence tables by all panel members. The strength of evidence supporting each drainage approach was graded using the following approach:

A. Randomized, controlled trials with consistent results or

individual randomized, controlled trial with narrow CI.
B. Controlled cohort and case-control series.
C. Historically controlled series and case series.
D. Expert opinion without explicit critical appraisal or based on physiology, bench research, or "first principles."

Results

Literature Review

The MEDLINE search yielded 789 citations. After review of these citations, their bibliographies, and citations from panel members' files, 24 articles were identified for full review by the panel. Included in these 24 articles were 3 randomized, controlled trials,[16–18] 2 historically controlled series,[19,20] and 19 case series.[21–39] The 3 randomized, controlled trials, 2 historically controlled series, and 14 of the case series presented results of primary management approaches to PPE; 5 of the case series[26,30,32,34,37] provided data on rescue approaches. Summaries of the design features and patient characteristics for the 3 randomized, controlled trials and the 2 historically controlled series and the 14 case series of primary management are in Tables 2 and 3, respectively. Altogether, data from 34 separate cohorts (ranging in

Table 2—*Design Features and Patient Characteristics of Randomized, Controlled Trials and Historically Controlled Series*

Trials	Cohorts	Setting	Patient Characteristics	PPE Category
Randomized, Controlled Trials				
Bouros et al[16]	1. Streptokinase (250,000 IU daily, duration determined by patient response), n = 25 2. Urokinase (100,000 IU daily), n = 25	Single site, Greece, 1990–1995	33 men, 17 women; median age, 47 yr (range, 15–92 yr) for cohort 1 and 51 yr (range, 17–89 yr) for cohort 2; numerous comorbid conditions; duration of prediagnosis symptoms not given	39 with category 3 and 11 with category 4
Davies et al[17]	1. Streptokinase (250,000 IU daily for 3 d), n = 12 2. Normal saline flush through tube thoracostomy, n = 12	Single site UK, mid 1990s	17 men, 7 women; mean (SD) age, 62 ± 23 yr for cohort 1 and 60 ± 23 yr for cohort 2; comorbid conditions not described; mean (SD) prediagnosis symptom duration of 27 ± 17 d for cohort 1 and 35 ± 26 d for cohort 2	13 with category 3 and 11 with category 4
Wait et al[18]	1. Streptokinase (250,000 IU daily for 3 d), n = 9 2. VATS, n = 11	Single site, US, 1994–1996	15 men, 5 women; mean (SD) age, 42 ± 20 yr for cohort 1 and 43 ± 13 yr for cohort 2; comorbid conditions not described; prediagnosis duration of symptoms not given	Not specified
Historically Controlled Series				
Chin and Lim[19]	1. Tube thoracostomy, n = 29 2. Streptokinase (250,000 IU daily, duration determined by patient response), n = 23	Single site, Singapore, 1990–1992 for cohort 1 and 1992–1995 for cohort 2	41 men, 11 women; mean (SD) age 63 ± 14 yr for cohort 1 and 50 ± 19 yr for cohort 2; comorbid conditions mostly diabetes and lung disease; prediagnostic duration of symptoms not given	12 with category 3 and 40 with category 4
Mackinlay et al[20]	1. Surgery, n = 33	Single site, Argentina, 1985–1991 for cohort 1 and 1992–1995 for cohort 2	43 men and 21 women; mean (SD) age, 51 ± 18 yr for cohort 1 and 49 ± 18 yr for cohort 2; comorbid conditions not described; pretreatment duration of effusion 17.5 d in cohort 1 and 11.4 d in cohort 2	Not specified

Table 3—*Design Features and Patient Characteristics of Case Series*

Case Series	Cohorts	Setting	Patient Characteristics	Category
Ali and Unruh[21]	1. Tube thoracostomy, n = 17 2. Surgery, n = 17	Single site, Canada, mid 1980s	Sex, age, comorbid conditions, and pretreatment duration of symptoms not provided	Not specified
Benfield[22]	1. No drainage, n = 23 2. Therapeutic thoracentesis, n = 24 3. Tube thoracostomy, n = 25	Single site, UK, 1968–1978	Sex, age, comorbid conditions, and pretreatment duration of symptoms not definable for PPE patients	Not specified
Berger and Morganroth[23]	1. Tube thoracostomy, n = 23 2. No drainage, n = 16	Single site, US, 1977–1987	Sex, age, and pretreatment duration of symptoms not provided for all patients. Serious comorbid conditions excluded	23 with category 3 and 13 with category 4
Cohn and Blaisdell[24]	1. Tube thoracostomy, n = 84	Single site, US, 1950–1968	Sex, age, comorbid conditions, and pretreatment duration of symptoms not provided for all patients	Not specified
Hoover et al[25]	1. Tube thoracostomy, n = 61	Single site, US, 1980–1986	39 men, 22 women; mean (SD) age, 34 ± 18 yr; comorbid conditions were substance abuse	Not specified
Lemmer et al[27]	1. Therapeutic thoracentesis, n = 4 2. Tube thoracostomy, n = 13 3. Surgery, n = 5	Single site, US, 1978–1982	Sex, age, comorbid conditions, and pretreatment duration of symptoms not definable for PPE patients	Not specified
Limthongkul et al[28]	1. Tube thoracostomy, n = 49	Single site, Thailand, 1987–1991	Sex, age, comorbid conditions, and pretreatment duration of symptoms not definable for PPE patients	30 with category 3 and 19 with category 4
Mandal and Thadepalli[29]	1. Therapeutic thoracentesis, n = 28 2. Tube thoracostomy, n = 43 3. Surgery, n = 41	Single site, US, 1972–1984	90 men, 22 women; mean age, 39 yr (range, 19–71 yr); comorbid conditions and pretreatment duration of symptoms not provided	Not specified
Mayo[31]	1. Surgery, n = 63	Single site, US, 1955–1979	52 men, 11 women; median age, 47 yr for patients without comorbidity; median age, 58 yr for patients with comorbidity (diabetes, heart or lung disease, and alcoholism); pretreatment duration of symptoms 2–8 wk for patients without comorbidity and 2–20 wk for patients with comorbidity	63 with category 4
Poe et al[33]	1. Tube thoracostomy, n = 21 2. No drainage, n = 22	Single site, US, 1987–1989	Sex, age, comorbid conditions, and pretreatment duration of symptoms not definable	Not specified
Roupie et al[35]	1. Tube thoracostomy, n = 37	Single site, France, 1993–1995	Sex, age, comorbid conditions, and pretreatment duration of symptoms not definable	Not specified
Storm et al[36]	1. Therapeutic thoracentesis, n = 51 2. Tube thoracostomy, n = 43	Single site, Denmark, 1984–1989	Cohort 1 had 37 men, 14 women, with mean age 58 yr; cohort 2 had 26 men, 17 women, with mean age 60 yr; most patients had comorbid illness, usually alcoholism; pretreatment duration of symptoms not provided	59 with category 3 and 35 with category 4
Vianna[38]	1. Therapeutic thoracentesis, n = 41	Single site, US, 1964–1968	Sex not provided; mean age of patients without comorbidity was 44 yr; mean age for patients with comorbidity (mostly alcoholism and lung disease) was 55 yr; pretreatment duration of symptoms not provided	Not specified
Wehr and Adkins[39]	1. Therapeutic thoracentesis, n = 27	Single site, US, 1974–1984	Sex, age, comorbid conditions, and pretreatment duration of symptoms not definable for PPE patients	Not specified

size from 4 to 84 patients) in the 19 articles could be categorized under the six possible primary management approaches.

The pooled proportion of deaths was higher for the no drainage (6.6%), therapeutic thoracentesis (10.3%), and tube thoracostomy management approaches (8.8%) than for the fibrinolytic (4.3%), VATS (4.8%), and surgery (1.9%) approaches, but the 95% CI showed considerable overlap among all six possible primary management approaches (Table 4 and Fig 1). The pooled proportion of patients needing a second intervention to manage the PPE was also higher for the no drainage (49.2%), therapeutic thoracentesis (46.3%), and tube thoracostomy (40.3%) management approaches than the fibrinolytic (14.9%), VATS (0%), and surgery (10.7%) approaches; there was no overlap in the 95% CI between the first three and the last three management approaches (Table 5 and Fig 2), indicating a nonrandom difference. There was considerable heterogeneity among cohort results for the two outcomes within each primary management approach (Figs 1 and 2).

Randomized, Controlled Trials

Each of the three randomized, controlled trials included at least one fibrinolytic treatment arm. Bouros et al[16] compared the efficacy and safety of two different fibrinolytics, streptokinase and urokinase, in the treatment of PPE. Fifty consecutive patients were randomly allocated to receive either

Table 4—*Proportion of Deaths With 95% CI in Individual Cohorts and Pooled by Primary Management Approach*

Author	Number at Risk	Number Died	Death Proportion, %	95% CI, %
No drainage	61	4	6.6	1.8, 16.0
Benfield[22]	23	2	8.7	1.1, 28.0
Berger and Morganroth[23]	16	1	6.3	0.2, 30.2
Poe et al[33]	22	1	4.5	0.1, 22.8
Therapeutic thoracentesis	175	18	10.3	6.2, 15.8
Benfield[22]	24	3	12.5	2.7, 32.4
Lemmer et al[27]	4	1	25.0	0.6, 80.6
Mandal and Thadepalli[29]	28	0	0.0	0.0, 12.4
Storm et al[36]	51	4	7.8	2.2, 18.9
Viana[38]	41	8	19.5	8.8, 34.9
Wehr and Adkins[39]	27	2	7.4	0.9, 24.3
Tube thoracostomy	408	36	8.8	6.3, 12.0
Ali and Unruh[21]	17	0	0.0	0.0, 19.5
Benfield[22]	25	4	16.0	4.5, 36.0
Berger and Morganroth[23]	23	4	17.4	5.0, 38.8
Chin and Lim[19]	29	7	24.1	10.3, 43.5
Cohn and Blaisdell[24]	84	9	10.7	5.0, 19.4
Davies et al[17]	12	0	0.0	0.0, 26.5
Hoover et al[25]	61	3	4.9	1.0, 13.7
Lemmer et al[27]	13	2	15.4	1.9, 45.5
Limthongkul et al[28]*	N/A	N/A	N/A	N/A
Mandal and Thadepalli[29]	43	2	4.7	0.6, 15.8
Poe et al[33]	21	1	4.8	0.1, 23.8
Roupie et al[35]	37	0	0.0	0.0, 9.5
Storm et al[36]	43	4	9.3	2.6, 22.1
Fibrinolytics	94	4	4.3	1.2, 10.5
Bouros et al[16]	25	0	0.0	0.0, 13.7
Bouros et al[41]	25	1	4.0	0.1, 20.4
Chin and Lim[19]	23	2	8.7	1.1, 28.0
Davies et al[17]	12	0	0.0	0.0, 26.5
Wait et al[18]	9	1	11.1	0.3, 48.2
VATS	42	2	4.8	0.6, 16.2
Mackinlay et al[20]	31	1	3.2	0.1, 16.7
Wait et al[18]	11	1	9.1	0.2, 41.2
Surgery	159	3	1.9	0.6, 16.2
Ali and Unruh[21]	17	0	0.0	0.0, 19.5
Lemmer et al[27]	5	0	0.0	0.0, 52.1
Mackinlay et al[20]	33	1	3.0	0.1, 15.8
Mandal and Thadepalli[29]	41	0	0.0	0.0, 8.6
Mayo[31]	63	2	3.2	0.4, 11.0

*Data on deaths not provided (N/A).

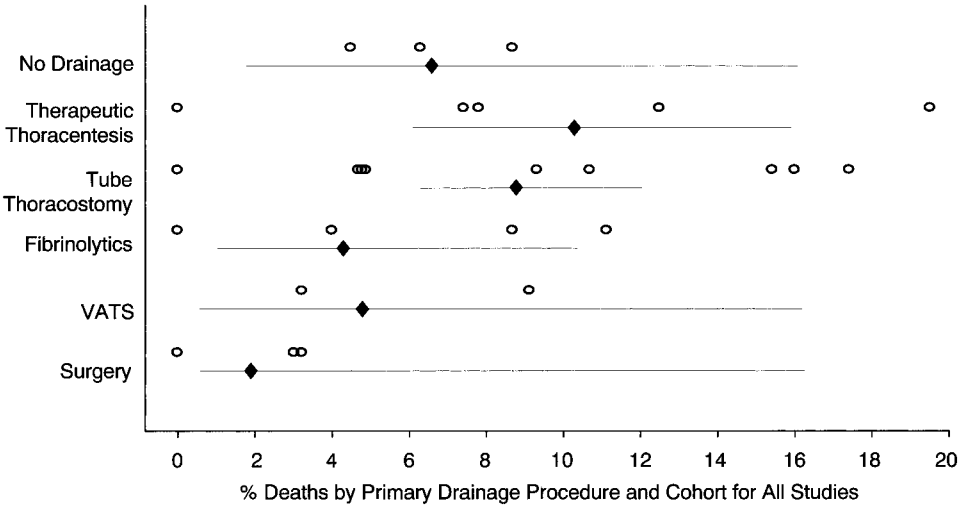

FIGURE 1. The proportion of patients dying within each individual cohort (○) and pooled across all studies (◆) is shown for each primary management approach. Horizontal lines extending from pooled estimates indicate 95% CI.

streptokinase (250,000 IU in 100 mL normal saline solution) or urokinase (100,000 IU in 100 mL normal saline solution) through tube thoracostomy in a double-blind fashion on a daily basis until the PPE resolved. Patients were assessed prospectively for changes in the chest radiograph, pleural fluid drainage, and clinical resolution. Each group was treated for approximately 6 days. There were similar improvements in the chest radiograph for both treatment groups during the course of the study. Pleural fluid drainage significantly increased with fibrinolytic therapy, and the increase in pleural fluid drainage was similar for patients treated with streptokinase and urokinase. Most patients in both treatment groups had marked clinical improvement with fibrinolytic therapy. Only two patients in each group required a second intervention to further manage the PPE, and only one patient died (in the urokinase group). The only difference noted in the clinical course between the two treatment groups was transient fever after streptokinase therapy in seven patients. The authors concluded that fibrinolytic therapy was an effective method for managing PPE, but that urokinase was preferred because of the lower incidence of drug-related adverse events.

Davies and colleagues[17] compared the effects of fibrinolytic therapy with tube thoracostomy in managing PPE. Twenty-four patients were randomized to receive either streptokinase (250,000 IU in 20 mL normal saline solution) or saline flush through tube thoracostomy daily for 3 days. The primary end points, prospectively assessed, were pleural fluid drainage and improvement in the chest radiograph. Secondary end points were time to defervescence, time to normalization of the WBC count, length of stay in the hospital, and number of procedures needed for effective pleural space drainage. There was significantly greater pleural fluid drainage and chest radiograph improvement in the group randomized to receive fibrinolytics. Three patients in the tube thoracostomy control group required a second intervention to effectively drain the pleural space vs none in the fibrinolytic group (not significant, $p = 0.109$). There were no significant differences between the two treatment groups in hospital length of stay, time to defervescence, and time to normalization of WBC count. There were no deaths in either group. Of note, no evidence of systemic fibrinolysis or bleeding complications was found with streptokinase therapy. The authors interpreted the data to indicate that fibrinolytics probably improved management of PPE by improving pleural fluid drainage.

Wait et al[18] compared the results after fibrinolytic therapy with VATS in the management of PPE. Twenty patients were randomly allocated to receive either streptokinase (250,000 IU in 100 mL normal saline solution) administered daily for 3 days through tube thoracostomy or immediate VATS. The primary end point was inadequate pleural space drainage assessed by chest radiography. Also prospectively monitored were clinical outcomes, length of hospital stay, and duration of chest tube drainage. The group treated with immediate VATS had a significantly higher treatment success rate (defined as a $> 50\%$ reduction in the original pleural fluid) than the fibrinolytic group. One patient in each treatment group died, but more patients receiving fibrinolytics

Table 5—*Proportion of Patients Needing a Second Intervention With 95% CI in Individual Cohorts and Pooled by Primary Management Approach*

Author	Number at Risk	Number With Second Intervention	Second Intervention Proportion, %	95% CI, %
No drainage	61	30	49.2	36.1, 62.3
Benfield[22]	23	17	73.9	51.6, 89.8
Berger and Morganroth[23]	16	2	12.5	1.6, 38.3
Poe et al[33]	22	11	50.0	28.2, 71.8
Therapeutic thoracentesis	175	81	46.3	38.7, 54.0
Benfield[22]	24	16	66.7	44.7, 84.4
Lemmer et al[27]	4	1	25.0	0.6, 80.6
Mandal and Thadepalli[29]	28	0	0.0	0.0, 12.4
Storm et al[36]	51	3	5.9	1.2, 16.2
Viana[38]	41	40	97.6	87.1, 99.9
Wehr and Adkins[39]	27	21	77.8	57.7, 91.4
Tube thoracostomy	434	175	40.3	35.7, 45.1
Ali and Unruh[21]	17	16	94.1	71.3, 99.9
Benfield[22]	25	13	52.0	31.3, 72.2
Berger and Morganroth[23]*	N/A	N/A	N/A	N/A
Chin and Lim[19]	29	4	13.8	3.9, 31.6
Cohn and Blaisdell[24]	84	43	51.2	40.0, 62.2
Davies et al[17]	12	3	25.0	5.5, 57.2
Hoover et al[25]	61	28	45.9	33.1, 59.2
Lemmer et al[27]	13	2	15.4	1.9, 45.5
Limthongkul et al[28]	49	8	16.3	7.3, 29.6
Mandal and Thadepalli[29]	43	4	9.3	2.6, 22.1
Poe et al[33]	21	4	19.0	5.5, 41.9
Roupie et al[35]	37	16	43.2	27.1, 60.5
Storm et al[36]	43	34	79.1	63.9, 89.9
Fibrinolytics	94	14	14.9	8.4, 23.7
Bouros et al[16]	25	2	8.0	1.0, 26.1
Bouros et al[41]	25	2	8.0	1.0, 26.1
Chin and Lim[19]	23	5	21.7	7.5, 43.7
Davies et al[17]	12	0	0.0	0.0, 26.5
Wait et al[18]	9	5	55.6	21.2, 86.3
VATS	42	0	0.0	0.0, 8.4
Mackinlay et al[20]	31	0	0.0	0.0, 11.2
Wait et al[18]	11	0	0.0	0.0, 28.5
Surgery	159	17	10.7	6.3, 16.6
Ali and Unruh[21]	17	12	70.6	44.0, 89.7
Lemmer et al[27]	5	0	0.0	0.0, 52.1
Mackinlay et al[20]	33	4	12.1	3.4, 28.2
Mandal and Thadepalli[29]	41	0	0.0	0.0, 8.6
Mayo[31]	63	1	1.6	0.0, 8.5

*Data on patients requiring a second intervention not provided (N/A).

than VATS required a second intervention to manage the PPE. The hospital length of stay and duration of chest tube drainage were significantly shorter in the VATS group than the fibrinolytic group. The authors concluded that VATS as the primary treatment strategy for PPE was more effective than fibrinolytic therapy.

Historically Controlled Series

The two historically controlled series did not include the same management approaches. Chin and Lim[19] analyzed the treatment responses of PPE to either tube thoracostomy or fibrinolytics. A historical control group, studied from 1990 to 1992, of 29 patients was treated with tube thoracostomy. A second group of 23 patients, evaluated from 1992 to 1995, was given streptokinase (250,000 IU in 100 mL normal saline solution) daily through tube thoracostomy. Outcome measures assessed were time to defervescence, duration of tube drainage, pleural fluid drainage, length of hospital stay, and clinical recovery. Baseline characteristics of the two groups were similar. There were no differences between the two groups in time to defervescence, days of chest tube drainage, and hospital stay, although the fibrinolytic group did have a greater amount of total pleural fluid drainage. The death rate was lower for the group treated with fibrinolytics but the need for

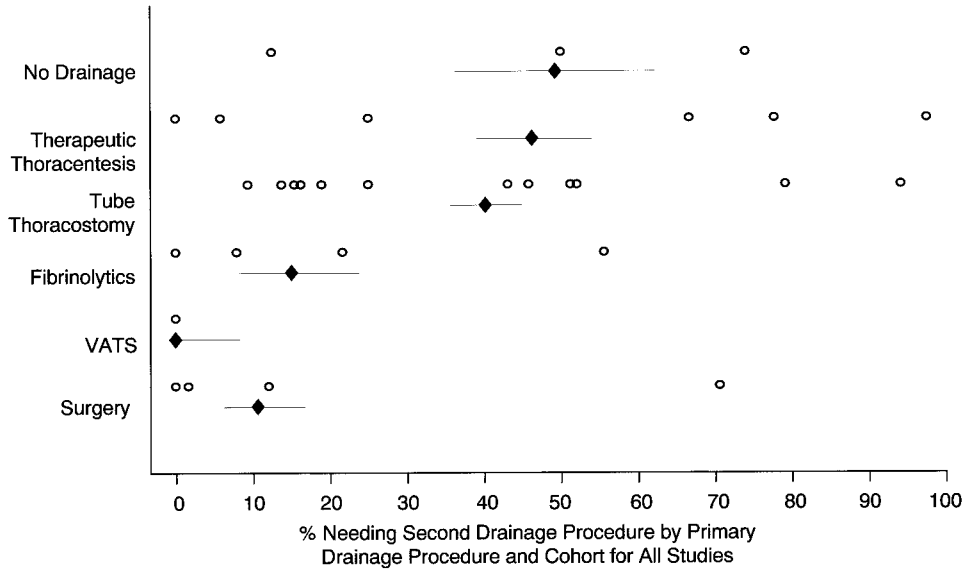

FIGURE 2. The proportion of patients requiring a second intervention to manage the PPE within each individual cohort (○) and pooled across all studies (◆) is shown for each primary management approach. Horizontal lines extending from pooled estimates indicate 95% CI.

a second intervention to drain the pleural space was similar for the two treatment groups. The authors stated that fibrinolytics increased pleural fluid drainage, but did not markedly improve clinical recovery from PPE compared with tube thoracostomy.

Mackinlay and colleagues[20] compared the outcomes after surgery and VATS for management of PPE. The historically controlled group included 33 patients treated between 1985 and 1991 by thoracotomy with or without rib resection. From 1992 to 1994, 31 patients with PPE underwent VATS. Duration of chest tube drainage, length of hospital stay, and clinical outcomes were evaluated. The groups were generally similar at baseline, except the historically controlled group had a significantly longer preoperative course than the VATS group. Duration of chest tube drainage and length of hospital stay were significantly shorter for the patients treated with VATS. There was one death in each treatment group; four patients in the historically controlled group and none in the VATS group required a second intervention to manage the PPE. The authors concluded that clinical outcomes were comparable for VATS and thoracotomy in managing PPE, but VATS offers advantages in terms of postoperative care.

Rescue Approaches

A summary of design features and patient characteristics for the five case series[26,30,32,34,37] presenting results of management approaches performed exclusively as a second, or rescue, intervention after failure of a previous management approach is in Table 6. Lawrence et al[26] reported the results of VATS performed in patients resistant to medical management of PPE, either therapeutic thoracentesis or tube thoracostomy. They found that VATS was successful in draining PPE in the majority of rescue situations. Performing VATS did not preclude conversion to other surgical procedures in unsuccessful cases. Pothula and Krellenstein[34] described a series of cases undergoing thoracotomy after incomplete resolution of the PPE with tube thoracostomy. Thoracotomy allowed effective drainage; limited thoracotomy, performed in extremely ill patients, was also effective. The patients presented by Martella and Santos[30] also underwent thoracotomy after inadequate drainage with tube thoracostomy. Decortication effectively controlled PPE, but 25% of patients required additional operative procedures to control ongoing lung infection. Morin et al[32] performed thoracotomy after numerous failed attempts at drainage of the PPE with tube thoracostomy. Management of PPE was successful in all cases, with prompt recovery. Temes and colleagues[37] described the results of fibrinolytic therapy in patients who had previously failed to respond to tube thoracostomy. Most patients (16/26 or 62%) had complete resolution of PPE with fibrinolytic therapy, but two patients (8%) had only partial resolution and required long-term empyema tube drainage, and eight patients (31%) did not improve with fibrinolytics and underwent surgery.

Table 6.—*Summary of Number of Deaths and Need for Further Interventions in Patients Undergoing Rescue Management of PPE*

Study	Rescue Procedure	Patient Characteristics	Outcomes, n (%)	Previous Treatment
Lawrence et al[26]	VATS, n = 42 Single site, UK, 1993–1996	Age on average, 50–53 yr, preoperative duration of symptoms on average, 37–40 d; sex, comorbidities, and category of PPE not given	Deaths, 0 (0) Further intervention, 12 (28.6)	Usually tube thoracostomy or therapeutic thoracentesis
Martella and Santos[30]	Surgery, n = 25 Single site, US, 1988–1990	Mean age, 41 yr (range, 25–72 yr); preoperative duration of symptoms on average, 57 d; 13 men, 12 women; numerous comorbidities (usually alcoholism); category of PPE not given	Deaths, 1 (4) Further intervention, 10 (40)	Tube thoracostomy
Morin et al[32]	Surgery, n = 20 Single site, Canada, 1964–1971	Age and preoperative duration of symptoms not given; 19 men, 4 women; comorbidities and category of PPE not given	Deaths, 0 (0) Further intervention, 0 (0)	Usually tube thoracostomy or therapeutic thoracentesis
Pothula and Krellenstein[34]	Surgery, n = 90 Single site, US, 1981–1992	Age and preoperative duration of symptoms not given; 73 men, 17 women; comorbidities and category of PPE not given	Deaths, 7 (7.8) Further intervention, 2 (2.2)	Usually tube thoracostomy or therapeutic thoracentesis
Temes et al[37]	Fibrinolytics (variable doses of either streptokinase or urokinase), n = 26 Single site, US, 1992–1994	Mean age, 41.8 ± 17.1 yr; mean preoperative duration of symptoms was 2.9 ± 2.6 wk; 23 men, 3 women; comorbidities and category of PPE not given	Deaths, 0 (0) Further intervention, 10 (38.5)	Tube thoracostomy

Quality Assessments

Methods of studies reporting results of primary management approaches to PPE were evaluated through assessment of six design features: inclusion of consecutive patients, active follow-up of outcomes, blinded assessments of outcomes, compliance to the treatment protocol, sample size calculations, and adequate description of criteria for performing rescue procedures. Thirteen of the 19 (68%) studies did not specify that consecutive patients were included, suggesting possible selection bias. Active follow-up with blinded assessment of outcomes was described in only two studies. In the case series, evaluation was retrospective and treatment protocols varied within the studies based on individual patient characteristics. Consequently, treatment bias could not be excluded. Sample size calculations were not reported in any study. Criteria for performing rescue procedures were usually not described in the case series, also suggesting possible treatment bias.

Discussion

The studies identified through a careful literature review as relevant to the medical and surgical management of PPE have significant methodological limitations. After decades of clinical interest in PPE, only three randomized, controlled trials have been performed, including < 100 patients, on the medical and surgical management of this problem. Most of the published material is derived from case series in which patient selection and treatment biases could not be excluded. These methodologic weaknesses resulted in heterogeneous data, precluded formal hypothesis testing and subgroup analyses, and limited the strength of any panel recommendations.

Evidence obtained from the literature review indicates that all six PPE management approaches have been effective in some patients. However, the panel was not able to define the patient characteristics that would indicate the likelihood for success with any of the individual management approaches. Furthermore, information about sequential use of PPE management approaches is limited. Despite the limitations in the data available, there did appear to be consistent and possibly clinically meaningful trends for the pooled data and the results of the randomized, controlled trials and the historically controlled series on the primary management approach to PPE. Based on these trends and consensus opinion, the panel recommends the following approach to managing PPE:

- In all patients with acute bacterial pneumonia, the presence of a PPE should be considered. Recommendation based on level C evidence.
- In patients with PPE, the estimated risk for

poor outcome, using the panel-recommended approach based on pleural space anatomy, pleural fluid bacteriology, and pleural fluid chemistry, should be the basis for determining whether the PPE should be drained. Recommendation based on level D evidence.

• Patients with very low (category 1) or low (category 2) risk for poor outcome with PPE may not require drainage. Recommendation based on level D evidence.

• Drainage is recommended for management of category 3 or 4 PPE based on the pooled data for mortality and the need for second interventions with the no drainage approach. Recommendation based on level C evidence.

• Based on the pooled data for mortality and the need for second interventions, therapeutic thoracentesis or tube thoracostomy alone appear to be insufficient treatment for managing most patients with category 3 or 4 PPE. Recommendation based on level C evidence. However, the panel recognizes that in the individual patient, therapeutic thoracentesis or tube thoracostomy, as planned interim steps before a subsequent drainage procedure, may result in complete resolution of the PPE. Careful evaluation of the patient for several hours is essential in these cases. If resolution occurs, no further intervention is necessary. Recommendation based on level D evidence.

• Fibrinolytics, VATS, and surgery are acceptable approaches for managing patients with category 3 and category 4 PPE based on cumulative data across all studies that indicate that these interventions are associated with the lowest mortality and need for second interventions. Recommendation based on level C evidence.

The panel urges that these recommendations be viewed cautiously because of the methodological problems described above. Especially important would be to avoid making definitive recommendations on the preferability of individual primary management approaches because of the limited available comparison data. For instance, a randomized, controlled trial showed that VATS is more effective than fibrinolytics,[18] and a historically controlled series showed that VATS is as effective as surgery and advantageous in terms of postoperative care.[20] However, the total number of patients included in these two studies was too small to support the conclusion that VATS is the preferable primary management approach for PPE. In addition, a randomized, controlled trial suggested that urokinase may be the preferred fibrinolytic because of a better side effect profile and similar efficacy as streptokinase, but the sample size was too small to reach a definitive recommendation.[16] (The panel notes that although urokinase is not available at present, personal communication with the manufacturer, Abbott Laboratories (Abbott Park, IL), indicates that this product should be available in the near future.) Only a small amount of data are available for approaches performed as rescue procedures, *ie*, after a primary management approach had failed to successfully control the PPE. Rescue approaches to PPE had a low mortality, but the need for further interventions after the rescue procedures to effectively control the PPE tended to be high. The most important observation from the panel may be that these findings could be a valuable foundation for designing a large, multicenter, randomized, controlled trial in this area.

The panel recognizes that this analysis was based on the consensus opinion that drainage of PPE should be performed only in patients with moderate (category 3) or high (category 4) risk for poor outcome. This approach differs from the traditional approach to categorizing PPE based on the three classic phases of empyema formation: the exudative stage, the fibropurulent stage, and the organizing stage. However, it had the advantage of ensuring that the panel recommendations were based entirely on data from patients with categories 3 and 4 PPE. Although it is intuitively reasonable that the first step in managing a PPE should be to estimate the risk for poor outcome, the method advised by the panel for risk categorization requires validation. The panel also recognizes that the clinical utility and decision thresholds (cutoff points) for prognostic variables included in this method, such as pleural fluid pH and glucose and size of the pleural effusion on chest radiograph, have not been well-established.

There were several clinically relevant issues that the panel had hoped to evaluate, but could not because of lack of adequate information. Data on the effect of various management options on secondary end points, such as time to defervescence, time to normalization of the WBC count, duration of drainage, length of hospital stay, and time to chest radiograph improvement, were rarely reported. Comparisons between small and large tube thoracostomy and tube thoracostomy insertion under radiographic guidance or percutaneously were not available. The panel had hoped to examine how this clinical practice guideline might be applied in other clinical situations, such as PPE in the lung cancer patient (particularly with an obstructing bronchial lesion), the patient with preexisting parenchymal lung disease (*eg*, interstitial lung disease), and the patient with lung parenchymal necrosis with or without a bronchopleural fistula. Unfortunately, insufficient data were available to support recommendations in these cases. Similarly, recommendations could not be proposed for special issues regarding antibiotic therapy in PPE (*eg*, the choice of antibi-

otic, the duration of antibiotic treatment, the dose of antibiotic, the use of intrapleural antibiotics, and the monitoring of antibiotic treatment). The panel did not explore how individual patient concerns might affect the choice among management options and the cost-effectiveness of the different management approaches.

Several observations from reviewing the methods of these studies are pertinent to designing future trials in this field. There was considerable variability in the surgical approaches to draining PPE. Most studies reported the results for thoracotomy,[20,29–32] but decortication and lung resection may have been performed as well. Results from rib resections were described in several series.[21,34,38] The timing of drainage procedures after diagnosis of PPE was not always made clear and probably varied widely among studies. Particularly of concern to the panel was the timing of sequential drainage approaches. A recent extension of a historically controlled series included in this analysis suggested that early surgery provided advantages in patients not responding rapidly to fibrinolytics.[40] The radiographic assessments performed before performing drainage procedures were usually not fully described. The panel urges that future studies be directed at better defining the surgical techniques, timing, and radiographic visualization of the pleural space needed for effective PPE drainage.

It should be noted that a recent study, not included in the literature review, support the recommendations of the panel. A small randomized, controlled trial compared fibrinolytics (n = 15) to tube thoracostomy (n = 16) in managing PPE.[41] No patients died in this series, but the fibrinolytic group needed a second intervention to manage the PPE significantly less often (2 of 15, or 13.5%) than the group receiving tube thoracostomy (12 of 16, or 75.0%). Of interest, in the group originally receiving tube thoracostomy, delayed use of fibrinolytics avoided surgery in only 6 of the 12 patients.

In summary, methodologic weaknesses in the clinical literature relevant to the medical and surgical management of PPE limit the strength of any recommendations by the panel. Trends in pooled data suggest that fibrinolytics, VATS, and surgery are acceptable approaches for managing PPE, but adequately designed randomized, controlled trials are urgently needed to further define the relative values of each of these procedures.

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