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# Primary Operative Versus Nonoperative Therapy for Pediatric Empyema: A Meta-analysis

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# Primary Operative Versus Nonoperative Therapy for Pediatric Empyema: A Meta-analysis

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**ABSTRACT.** *Objective.* **The optimal treatment of children with empyema remains controversial. The purpose of this review was to compare reported results of nonoperative and primary operative therapy for the treatment of pediatric empyema.**

*Methods.* **A systematic comprehensive review of the scientific literature was conducted with the PubMed (National Library of Medicine) database for the period from 1981 to 2004. This reproducible search identified all publications dealing with treatment of empyema in the pediatric population (<18 years of age). A meta-analysis was performed with studies with adequate data summaries for ≥1 of the outcomes of interest for both treatment groups.**

*Results.* **Sixty-seven studies were reviewed. Data were aggregated from reports of children initially treated nonoperatively (3418 cases from 54 studies) and of children treated with a primary operative approach (363 cases from 25 studies). The populations were similar in age. Patients who underwent primary operative therapy had a lower aggregate in-hospital mortality rate (0% vs 3.3%), reintervention rate (2.5% vs 23.5%), length of stay (10.8 vs 20.0 days), duration of tube thoracostomy (4.4 vs 10.6 days), and duration of antibiotic therapy (12.8 vs 21.3 days), compared with patients who underwent nonoperative therapy. In 8 studies for which meta-analysis was possible, patients who received primary operative therapy were found to have a pooled relative risk of failure of 0.09, compared with those who did not. Meta-analysis could not be performed for any of the other outcome measures investigated in this review. Similar complication rates were observed for the 2 groups (5% vs 5.6%).**

*Conclusions.* **These aggregate results suggest that primary operative therapy is associated with a lower in-hospital mortality rate, reintervention rate, length of stay, time with tube thoracostomy, and time of antibiotic therapy, compared with nonoperative treatment. The meta-analysis demonstrates a significantly reduced relative risk of failure among patients treated operatively.** ***Pediatrics*** **2005;115:1652–1659;** ***empyema, treatment, video-assisted thoracoscopic surgery, thrombolytics, thoracotomy.***

ABBREVIATIONS. VATS, video-assisted thoracoscopic surgery; MeSH, Medical Subjects Heading.

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Empyema affects nearly 1 of every 150 children hospitalized with pneumonia,[1] ranging in incidence from 0.4 to 6 cases per 1000 pediatric admissions.[2] Although empyema is a common entity, its management remains controversial. Therapeutic options include antibiotics, thoracentesis,[3] thoracostomy tube,[4,5] fibrinolytics,[6,7] video-assisted thoracoscopic surgery (VATS),[8,9] and thoracotomy.[10,11] Treatment measures are often used in a stepwise manner. The role of primary operative therapy has yet to be determined.

Empyema is a dynamic process that progresses through 3 stages.[12] Stage 1, the early exudative phase, involves a collection of thin reactive fluid and few cells in the pleural space. Stage 2 is the fibropurulent phase, with large quantities of white cells and fibrin deposition, which results in the formation of loculations. Stage 3 is the organizing phase, in which a thick fibrinous peel encases the lung, limiting its mobility. Although drainage with tube thoracostomy (chest tube) and antibiotics may be adequate for stage 1 disease, the presence of loculations and fibrinous adhesions may limit the success of this therapy.

Empyema is most often treated with primary nonoperative therapy (defined as antibiotics and thoracentesis/chest tube drainage). This approach is associated with prolonged hospitalization and frequent failure, requiring salvage operative interventions. Many series have demonstrated that children who experience failure of nonoperative therapy exhibit improvement after thoracotomy or VATS,[13–15] especially if the procedure is performed early.[16,17] On the basis of these results, many pediatric surgeons have come to consider primary operative therapy a more effective and efficient approach for treating children with empyema.[8] However, there are limited data to guide this consideration. The purpose of this study was to review systematically the outcomes from published reports of cases of primary operative therapy and nonoperative therapy, to better assess the role of primary operative therapy in the treatment of children with empyema.

## METHODS

### Study Design

A systematic comprehensive review of the scientific literature was conducted with the PubMed (National Library of Medicine) database for the period from January 1981 to October 2004. These dates range from the first reports of VATS in the pediatric population to the present.[15] This reproducible search identified all publications involving nonoperative or operative treatment of

empyema in the pediatric population (age: 0–18 years). Institutional review board approval was not required for this project.

### Search Strategy

The search strategy was conducted using the following 6 search strategies; searches 1 to 4 were limited to all children, 0 to 18 years, English: (1) Medical Subjects Heading (MeSH) "empyema, pleural" with subheadings complications OR drug therapy OR mortality OR prevention and control OR surgery OR therapy; limited to clinical trial (publication type) OR (NOT MeSH "case reports" AND [publications types metanalysis OR practice guidelines OR review OR MeSH "epidemiologic methods"]); (2) MeSH "pleural effusion" with subheadings complications OR drug therapy OR mortality OR prevention and control OR surgery OR therapy; limited to clinical trial (publication type) OR (NOT MeSH "case reports" AND key word parapneumonic); (3) MeSH "empyema" (major heading, no explosion) AND MeSH "empyema" (MeSH, no explosion) with subheadings drug therapy OR surgery OR therapy AND key word pleural OR parapneu* AND (NOT MeSH "case reports"); (4) MeSH "empyema, pleural" (MeSH) OR ("empyema" [MeSH, no explosion] AND "pleural diseases" [MeSH]) AND ("thrombolytic therapy" OR "fibrinolytic agents" OR "fibrinolytic agents" [pharmacological action]); (5) key words fibrinolytic* AND empyema AND (child* OR infant* OR pediatric* OR pediatric* OR adolescen* OR teen*); (6) key words empyema* AND (child* OR infant* OR pediatric* OR pediatric* OR adolescen* OR teen*) limited to in process titles.

### Inclusion Criteria/Exclusion Criteria

The search was limited to studies among children (0–18 years of age) published in the English language. Case reports, abstracts only, letters, reviews, and incomplete reports (studies that did not specify ≥1 outcomes of interest among children with empyema) were excluded. Studies that included only patients who experienced failure of nonoperative therapy were excluded from this analysis. Studies that included patients who were treated nonoperatively with salvage fibrinolytic therapy were included in this study. Data were also collected for patients treated with primary fibrinolytic therapy and were classified separately. In studies that described patients who underwent primary operative therapy, it was stated clearly that patients underwent the operative intervention before thoracentesis or tube thoracostomy. In studies that compared different primary therapeutic modalities, data were collected for groups of children who received either nonoperative or primary operative therapy only if the number of patients and ≥1 of the outcomes of interest were reported clearly for that treatment group.

### Search Yield

Two hundred eighteen publications were detected. Case reports, abstracts, incomplete reports, studies with adults, and reviews were excluded ($n = 151$). Sixty-three articles were reviewed, and citations from those reports were used to identify additional studies ($n = 26$), of which 4 met the inclusion criteria for this review. A single investigator, using criteria that were established before study initiation, reviewed 67 studies, and experts in data aggregation, statistical analysis, and pediatric surgery reviewed the study data.

### Definitions

#### *Primary Nonoperative Therapy*

Primary nonoperative therapy was defined as children being treated initially with antibiotics and thoracentesis and/or tube thoracostomy.

#### *Primary Operative Therapy*

Primary operative therapy was defined as children being treated initially with antibiotics and either VATS or thoracotomy.

#### *Primary Fibrinolytic Therapy*

Primary fibrinolytic therapy was defined as children being treated with fibrinolytics either at the time of or shortly after (<24 hours) tube thoracostomy. Fibrinolytics were defined as agents causing dissolution of fibrin through enzymatic activity and included most commonly urokinase and streptokinase.

### Outcomes

Adverse outcomes included the in-hospital mortality rate, therapeutic failure rate, length of hospitalization, total days with tube thoracostomy, total days with antibiotic therapy, and complication rate. All of these outcomes had consistent definitions across all studies, with the exception of complication rate. Failure rate was defined as failure of a primary intervention necessitating subsequent operative intervention. Conversion of a primary VATS to a thoracotomy was not considered a failure but was accounted for in the results. For both nonoperative therapy and primary operative therapy, complications typically included pneumothorax, bronchopleural fistula, persistent or recurrent empyema, bleeding, and wound infection. In some series, ICU admissions were considered complications and were included in the complication rate. Other series reported ICU stays as routine care, and such stays were excluded as complications in those studies. Because there were few standard definitions of complications and most authors did not provide definitions of complications, overall aggregate complication rates, as described by the authors, were calculated.

### Analyses

The proportions of patients who died, who underwent reoperation, and who experienced complications were calculated for children with empyema treated with nonoperative or primary operative therapy. The average age, total number of hospital days, total chest tube days, and total days with antibiotic therapy were also determined. In aggregations of data, the denominator for each evaluation was derived from the total number of cases in those studies that included the outcome being evaluated. A subset analysis of the results published in the past 5 years (1999–2004) was performed to evaluate the effects of advances in the treatment of empyema over time.

We conducted a formal meta-analysis of the differences between patients treated nonoperatively and those treated operatively. Of the 67 studies reviewed, 13 contained adequate data summaries for ≥1 of the outcomes of interest for both treatment groups (primary operative therapy and primary nonoperative therapy). Outcomes analyzed statistically included the mortality rate, failure rate, length of hospital stay, days with chest tube inserted, and duration of antibiotic therapy. For continuous outcomes (length of stay, days with chest tube inserted, and duration of antibiotic therapy), only studies that reported the number of subjects and the outcome mean and SD for all treatment groups were included. Studies that reported incomplete summaries and those that reported nonparametric summaries (median and interquartile range) were excluded from analysis. All of these 13 studies were published since 1999. Only 1 study[8] stated that patients in the primary operative therapy group were separated in time from patients in the primary nonoperative therapy group.

All meta-analyses were performed with Stata software (Stata Corp, College Station, TX), as described by Egger et al.[18] For binary outcomes, Mantel-Haenszel relative risk estimates were obtained for each study and were pooled across studies. For continuous outcomes, standardized mean differences were calculated within each study and pooled. For all meta-analyses, a $\chi^2$ test of heterogeneity across studies was performed to test for significant inconsistencies in the findings. Begg's test for publication bias was also performed.[19]

## RESULTS

### Nonoperative Therapy

Outcome data for children with empyema treated with initial nonoperative therapy ($n = 3418$) were derived from 54 studies (Table 1). The aggregate mortality rate was 3.3% (range: 0–35%), based on 3250 cases for which such data were available (50 studies), with a failure rate of 23.6% (range: 0–67%) in 2793 cases (44 studies) and a complication rate of 5.6% (range: 0–45%) in 1094 cases (22 studies). The average age of the nonoperatively treated cohort was 5 years (SD: ±1.5 years), based on data from 1792

**TABLE 1.** Outcomes of Nonoperative Therapy Among Children With Empyema

| Source | Year | No. of Subjects | No. of Deaths | No. of Failures | Length of Stay, d | Chest Tube, d |
|---|---|---|---|---|---|---|
| Weinstein et al[38] | 2004 | 23 | NS | NS | NS | 15 |
| Eroğlu et al[39] | 2004 | 81 | 0 | 6 | 24.3 | 11.9 |
| Karaman et al[40] | 2004 | 15 | 0 | NS | 15.4 | 13.5 |
| Singh et al[41] | 2004 | 38 | 0 | 8 | NS | NS |
| Ulku et al[42] | 2004 | 78 | 1 | 37 | NS | 12.75 |
| Yao et al[7] | 2004 | 22 | 0 | 9 | 18.2 | NS |
| Satish et al[4] | 2003 | 14 | 0 | 0 | 14 | 8 |
| Baranwal et al[43] | 2003 | 243 | 4 | 48 | 21.7 | 9.5 |
| Hilliard et al[11] | 2003 | 22 | 0 | 3 | 15 | NS |
| Caksen et al[44] | 2003 | 41 | 1 | NS | 27.9 | NS |
| Chen et al[31] | 2003 | 16 | 0 | NS | 24.3 | NS |
| Margenthaler et al[45] | 2003 | 33 | 0 | 16 | 14.1 | 11.6 |
| Chen et al[22] | 2003 | 37 | 0 | 24 | 33.2 | 15.2 |
| Cohen et al[8] | 2003 | 54 | 0 | 21 | 15.4 | 10.2 |
| Shoseyov et al[3] | 2002 | 67 | 0 | 5 | 24.2 | NS |
| Pierrepoint et al[32] | 2002 | 16 | 0 | 8 | 13.7 | 7.8 |
| Huang et al[46] | 2002 | 54 | 0 | 32 | 13 | 7.2 |
| Yilmaz et al[5] | 2002 | 46 | 1 | 2 | 28 | 12.2 |
| Chen et al[47] | 2002 | 58 | 0 | 39 | 12.4 | NS |
| Mitri et al[48] | 2002 | 67 | 0 | 18 | 6.5 | 5 |
| Doski et al[9] | 2000 | 98 | 0 | 44 | 11.6 | 4.2 |
| Chan et al[49] | 2000 | 47 | 0 | 21 | 15.4 | 8 |
| Meier et al[23] | 2000 | 27 | 0 | 4 | 14.6 | NS |
| Kercher et al[24] | 2000 | 3 | 0 | 2 | 16.6 | 12.3 |
| Shankar[33] | 2000 | 15 | 0 | NS | NS | NS |
| Hailu[50] | 2000 | 38 | 6 | 7 | 32 | NS |
| Patton et al[27] | 1999 | 11 | 0 | 0 | 13 | 8 |
| Sarihan et al[51] | 1998 | 52 | 0 | 5 | NS | 16.4 |
| Chan et al[52] | 1997 | 39 | 0 | 7 | 23.1 | NS |
| Hardie et al[53] | 1996 | 41 | 0 | 28 | NS | 7 |
| Maziah et al[54] | 1995 | 31 | 0 | 4 | 20.7 | 13 |
| Eren et al[14] | 1995 | 137 | 0 | 66 | 46.1 | NS |
| Fontanet et al[55] | 1993 | 98 | 1 | 4 | 30 | 11.9 |
| Mangete et al[56] | 1993 | 52 | 2 | 1 | NS | NS |
| Gocmen et al[57] | 1993 | 72 | 0 | 3 | 9 | 6 |
| Fujita et al[58] | 1992 | 20 | 7 | NS | NS | 13.1 |
| Mahalu and Nathoo[59] | 1992 | 52 | 0 | 2 | NS | NS |
| Hassan and Mabogunje[60] | 1992 | 100 | 14 | 10 | NS | NS |
| Asindi et al[61] | 1992 | 48 | 3 | NS | NS | NS |
| Kennedy et al[62] | 1991 | 31 | 0 | 8 | NS | NS |
| Hoff et al[63] | 1991 | 49 | 1 | 26 | 18.7 | 9.5 |
| Ghosh et al[64] | 1990 | 41 | 7 | NS | 15.8 | 9.6 |
| Gupta et al[65] | 1989 | 91 | NS | 13 | NS | NS |
| Golladay and Wagner[66] | 1989 | 27 | 2 | 10 | 28.3 | NS |
| Hoff et al[67] | 1989 | 51 | 1 | 18 | 18.5 | 10.2 |
| Alp et al[68] | 1988 | 175 | 2 | 35 | NS | 18.1 |
| Solak et al[69] | 1987 | 120 | 3 | 30 | NS | NS |
| Beg et al[70] | 1987 | 65 | 4 | 8 | NS | NS |
| Fajardo et al[71] | 1987 | 104 | 8 | NS | NS | NS |
| McLaughlin et al[72] | 1984 | 16 | 0 | 3 | 25 | 10 |
| Adeyemo et al[73] | 1984 | 298 | 15 | 2 | NS | NS |
| Freij et al[74] | 1984 | 227 | 19 | NS | NS | NS |
| Anyanwu et al[75] | 1983 | 91 | 6 | 23 | NS | NS |
| Anyanwu[76] | 1982 | 21 | 0 | 0 | NS | NS |

NS indicates not specified.

cases (37 studies). The average hospital stay for this group was 20 ± 8.3 days, based on data from 1671 cases (33 studies). The average length of tube thoracostomy was 10.6 ± 3.4 days, based on data from 1566 cases (28 studies). Antibiotics were used for an average of 21.3 ± 7.9 days, based on data from 381 cases (12 studies). For patients who failed nonoperative therapy, thoracotomy was performed for 76.7%, VATS was performed for 11.2%, and treatment was not specified in the remainder of cases.

### Fibrinolytic Therapy

Fibrinolytic therapy as a primary treatment for empyema was reported in 64 cases (3 studies).[6,7,11] Analysis of aggregate data on this technique revealed no in-hospital deaths, with a failure rate of 9.3% (range: 6.7–14.2%), based on 64 cases (3 studies), and a complication rate of 12.5% (range: 0–16.6%), based on 64 cases (3 studies). The average length of stay was 10.6 ± 5.1 days, based on 64 cases (3 studies).

### Primary Operative Therapy

Outcome data for children with empyema treated with primary operative therapy ($n$ = 363) were reported in 25 cases (Table 2). There were no reported perioperative deaths. A failure rate of 2.5% (range: 0–12.5%) and a complication rate of 5% (range:

**TABLE 2.** Outcomes of Primary Operative Therapy Among Children With Empyema

| Source | Year | No. of Subjects | No. of Deaths | No. of Failures | Length of Stay, d | Chest Tube, d |
|---|---|---|---|---|---|---|
| Ozcelik et al[77] | 2004 | 9 | NS | NS | 10.4 | NS |
| Eroğlu et al[39] | 2004 | 12 | 0 | 0 | 11 | NS |
| Karaman et al[40] | 2004 | 15 | 0 | NS | 9.5 | 7.5 |
| Kalfa et al[20] | 2004 | 4 | 0 | 0 | 11.8 | 6.2 |
| Knudtson and Grewal[21] | 2004 | 21 | 0 | 2 | 13 | 3 |
| Chen et al[22] | 2003 | 18 | 0 | 0 | 21.5 | 5.3 |
| Alexiou et al[10] | 2003 | 36 | 0 | 4 | 5 | NS |
| Hilliard et al[11] | 2003 | 24 | 0 | 0 | 6.5 | NS |
| Chen et al[31] | 2003 | 23 | 0 | NS | 24.5 | NS |
| Cohen et al[8] | 2003 | 21 | 0 | 0 | 7.4 | 4 |
| Pierrepoint et al[32] | 2002 | 7 | 0 | 0 | 9.5 | 5 |
| Chen et al[47] | 2002 | 12 | 0 | NS | 8 | NS |
| Doski et al[9] | 2000 | 41 | 0 | 1 | 7 | 3 |
| Meier et al[23] | 2000 | 4 | 0 | 0 | 11.5 | NS |
| Kercher et al[24] | 2000 | 13 | 0 | 2 | 8.3 | 4.2 |
| Rodriguez et al[25] | 2000 | 7 | 0 | 0 | 11.5 | 3.1 |
| Shankar et al[33] | 2000 | 25 | 0 | 0 | NS | NS |
| Merry et al[26] | 1999 | 19 | 0 | 0 | 10.3 | 2.9 |
| Patton et al[27] | 1999 | 3 | 0 | 0 | NS | NS |
| Grewal et al[28] | 1999 | 19 | 0 | 0 | NS | NS |
| Gandhi and Stringel[29] | 1997 | 6 | 0 | 0 | NS | NS |
| Rizalar et al[34] | 1997 | 7 | 0 | 0 | NS | NS |
| Khakoo et al[35] | 1996 | 5 | 0 | 0 | 8.4 | NS |
| Stovroff et al[30] | 1995 | 2 | 0 | 0 | 10 | NS |
| Kosloske and Cartwright[36] | 1988 | 10 | 0 | 0 | NS | NS |

NS indicates not specified.

0–15.3%) were reported, based on 304 cases (22 studies) and 258 cases (17 studies), respectively. The average age of the primarily operatively treated cohort was 5.5 ± 1.3 years, based on 287 cases (19 studies). The average length of stay was 10.8 ± 4.8 days, based on 293 cases (22 studies). The average length of time the thoracostomy tube remained in place was 4.4 ± 1.6 days, based on 161 cases (10 studies). Antibiotics were used for an average of 12.8 ± 3.8 days, based on 68 cases (5 studies). VATS was performed for 48.4% and thoracotomy was performed for 48.2% of patients with primary operative therapy. One study did not specify the mode of primary operative therapy and accounted for the remaining 3.4% of children with primary operative therapy.

These data were stratified with respect to patients who underwent VATS ($n$ = 176 in 13 studies)[8,9,20–30] or thoracotomy ($n$ = 175 in 12 studies)[10,11,27,31–36] as the primary operative intervention. Patients with primary VATS had a conversion rate to thoracotomy of 1.1% and a failure rate of 2.8% ($n$ = 176 in 13 studies). Children with primary thoracotomy underwent reoperation in 3.1% of cases ($n$ = 128 in 9 studies). A summary of outcomes for primary VATS versus primary thoracotomy demonstrates that reported outcomes were consistently better for the operative therapy group, despite suggestions in the reported studies that operatively treated patients had more advanced disease (Table 3).

Because more studies of primary nonoperative management than primary operative therapy were performed before 1995, we performed a subset analysis of results published in the past 5 years. This subset analysis demonstrated that, although mortality rates for nonoperatively treated patients decreased over time (1.0% in the latest era), the failure rate of nonoperative therapy was still considerable (30.7%) and much higher than the operative failure

**TABLE 3.** Summary of Outcomes for Primary Operative Treatment Versus Nonoperative Treatment of Empyema Among Children

| | Nonoperative Therapy | | Primary Operative Therapy ($n$ = 363)* | |
|---|---|---|---|---|
| | Chest Tube and Antibiotics ($n$ = 3183) | Primary Fibrinolytic Therapy ($n$ = 64) | VATS ($n$ = 176) | Thoracotomy ($n$ = 175) |
| Age, y (cases/studies) | 5 (1691/35) | 4.1 (64/3) | 5.1 (176/13) | 6.7 (99/6) |
| Mortality rate, % (cases/studies) | 3.3 (3250/50) | 0 (64/3) | 0 (176/13) | 0 (166/11) |
| Failure rate, % (cases/studies) | 23.6 (2793/44) | 9.4 (64/3) | 2.8 (176/13) | 3.1 (128/9) |
| Length of stay, d (cases/studies) | 20.0 (1671/33) | 10.7 (64/3) | 11.2 (150/10) | 10.6 (122/8) |
| Chest tube, total d (cases/studies) | 10.6 (1566/28) | 4 (14/1) | 4 (144/8) | 6.2 (22/2) |
| Antibiotics, d (cases/studies) | 21.3 (381/12) | NS | 13.2 (56/4) | NS |
| Complication rate, % (cases/studies) | 5.6 (1094/22) | 12.5 (64/3) | 5.4 (168/11) | 5.2 (77/5) |

NS indicates not specified.
* The mode of primary surgery was not specified for 3.4% of patients who underwent primary surgery.

rate (3.3%). The length of hospitalization was 1 week longer for nonoperatively treated patients, compared with operatively treated patients, in this latest era (18 and 11 days, respectively).

A meta-analysis of outcomes for nonoperative and operative therapy was performed. Table 4 gives the number of articles that had usable data for each outcome. Mortality rates could not be evaluated in this way because no deaths were observed in either treatment group in any of these reports. Only failure rates were reported in a sufficient number of articles to allow for a formal meta-analysis. In all 8 studies included in this meta-analysis, patients who received primary operative therapy had a lower risk of failure, compared with those who did not (Fig 1). In the 3 largest of these studies, the relative risk of failure was significantly less than 1 ($P < .05$). Overall, the pooled relative risk of failure among these patients was highly significant at 0.09 ($P < .0001$). A $\chi^2$ test did not show significant evidence of heterogeneity ($P = .60$) across studies, but Begg's test showed evidence of publication bias ($P < .05$). The meta-analysis was inconclusive for the remaining outcomes, because there were few articles and a large degree of heterogeneity across studies. There were no studies that compared VATS with thoracotomy.

## DISCUSSION

In this comprehensive review of the published literature, aggregate analysis of reported outcomes for patients who underwent primary nonoperative treatment demonstrated prolonged hospitalizations, a greater need for reintervention, and a higher mortality rate, compared with patients who underwent primary operative or fibrinolytic therapy. The failure rate for patients treated with primary fibrinolytic therapy was lower than that for patients treated nonoperatively but higher than that for patients treated with primary operative therapy. Primary fibrinolytic therapy also appeared to have a higher reported complication rate than treatment with primary nonoperative or operative therapy. The mortality and complication rates reported for the primary operative intervention group did not differ between patients who underwent VATS versus thoracotomy. The meta-analysis comparing rates of treatment failure across 8 studies suggested that the failure rate was ~11 times higher in the primary nonoperative therapy group, compared with the primary operative therapy group.

**TABLE 4.** Description of Data Subset Available for Meta-analysis

| Outcome | Articles | Nonoperative Patients | Operative Patients |
|---|---|---|---|
| Mortality rate* | 13 | 453 | 218 |
| Failure rate† | 9 | 349 | 143 |
| Length of stay | 4 | 122 | 77 |
| Chest tube (total) | 3 | 106 | 54 |
| Chest tube (after procedure)‡ | 1 | 54 | 21 |
| Antibiotics | 2 | 91 | 39 |

* No deaths occurred in this subset; therefore, no analysis of mortality rates could be performed.
† No failure events occurred in 1 study, which left 8 articles available for meta-analysis.
‡ With only 1 article, no analysis could be performed.

Findings in this review indicate that primary operative therapy decreases the length of hospitalization and has a lower failure rate. However, >76% of patients who undergo primary nonoperative therapy experience resolution of the disease without operative intervention. Although this relatively high success rate favors a stepwise approach to management, a less invasive primary operative intervention has the potential to interrupt the progression of empyema, to eliminate the increased pain and discomfort associated with prolonged thoracostomy tube use, and to reduce hospital stays by avoiding salvage operative therapy. In centers that use general anesthesia for chest tube placement, the use of VATS may be more appropriate, given the comparable effectiveness of VATS with respect to nonoperative therapy and the similar utilization of resources. More evidence is needed to determine whether management of pediatric empyema with primary operative therapy leads to improved outcomes. The limitations of this retrospective evaluation demonstrate the importance of a prospective, randomized trial evaluating stage-specific disease to answer this question.

Similarly, fibrinolytics (streptokinase and urokinase) have become part of the armamentarium for treatment of pediatric empyema. In the past 50 years, the majority of experience with fibrinolytic therapy has been among adults. In most of the pediatric studies reviewed, fibrinolytic therapy was used for children who failed to exhibit improvement with nonoperative therapy alone. In fact, salvage fibrinolytic therapy may cause worsening of intrapleural loculations and increase the difficulty of the VATS procedure.[37] Three studies in this review used fibrinolytics as a primary therapy, with a reduction in the failure rate but a higher reported complication rate, compared with primary nonoperative therapy.

Other issues may play a role in the selection of one therapeutic approach over another. Meier et al[23] reported a retrospective cost analysis and found that the costs for patients treated with intensive nonoperative therapy (>2 chest tubes) were 3 times as great as those for patients whose empyema was treated adequately with ≤2 chest tubes. This suggested that simple empyema could be treated with nonoperative measures in a cost-effective manner. However, prolonged chest tube drainage correlated with progression of the empyema, resulting in subsequent surgery and added expense. When patients treated with primary VATS were compared with children treated nonoperatively or with salvage VATS, primary VATS appeared to be more cost-effective than salvage VATS or nonoperative treatment for patients who required >2 chest tubes.

This review has several limitations. For example, one important variable in therapeutic decision-making is the stage of disease. Unfortunately, many studies in this review did not detail stage-specific results. Although nonoperative therapy may be successful for the treatment of stage 1 disease, the characteristic loculations and pleural peel found in late-stage disease make adequate drainage of the infected pleural

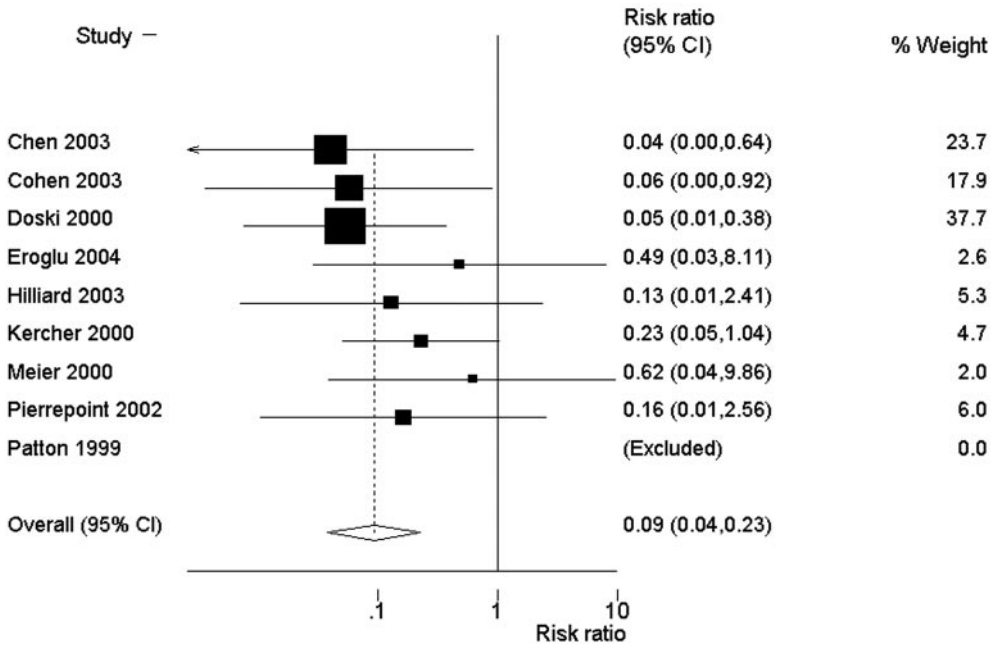


**Fig 1.** Forest plot of risk ratio estimates for failure rate among patients who receive primary operative therapy, compared with those who do not. The vertical line at 1 represents no difference between treatment groups. The center of each square is located at the risk ratio estimate for each study, and the area of each square reflects the weight given to that study in this meta-analysis. Horizontal lines show 95% confidence intervals for the risk ratio in each study. The dashed vertical line shows the pooled risk ratio estimate, and the width of the diamond gives the 95% confidence interval of this estimate.

space and expansion of the lung through simple drainage more difficult. It is unclear whether the 23% treatment failure rate found for the group of patients treated with tube thoracostomy drainage and antibiotics represented data for a patient population with stage 2 or 3 disease. Conversely, although patients undergoing operative therapy can be presumed to have advanced disease, operative success might be linked to an earlier stage of disease, in the absence of stage-specific data. The lack of stage-specific data complicates statistical comparisons of outcomes across treatment groups. Furthermore, many of the studies were not randomized trials, and the meta-analysis was subject to all of the selection biases that might be present in those studies. Criteria for selection of therapy likely evolved with time; the care of empyema among children has progressed in the past 20 years, with the inclusion of fibrinolytics and VATS. This creates a potential limitation for comparisons of VATS with nonoperative treatment. For this reason, we performed an aggregate analysis of reported outcomes from studies published in the past 5 years, and we found little impact on the outcome variables during that time. In the meta-analysis, the significant reduction in the failure rate was driven by the 3 largest studies in the analysis.[8,9,22] The benefit of operative therapy might be somewhat inflated in the study by Cohen et al,[8] because all primary nonoperative cases were taken from 1989–1997, whereas all primary operative cases were taken from 2000–2001, which means that the findings might be confounded by time differences. The less-invasive nature of VATS, compared with thoracotomy, might have caused a reduction in the threshold to proceed to operative intervention for patients who experienced failure of nonoperative therapy, resulting in an artificially elevated failure rate. In institutions with limited resources, patients treated nonoperatively might have had a low failure rate, resulting in prolonged hospitalization. A publication bias would exist if results were reported after proficiency in the operative technique had been obtained, falsely improving outcomes. In the meta-analysis evaluating failure rates, Begg's test gave a significant result, suggesting the possibility of publication bias (if not providing conclusive evidence of it).

## CONCLUSIONS

This systematic review of pediatric empyema outcomes demonstrated that primary operative therapy compared favorably with nonoperative approaches. In the aggregate analysis of the data, primary operative therapy was associated with a lower mortality rate, lower reintervention rate, shorter length of hospitalization, decreased time with a thoracostomy tube, and shorter course of antibiotic therapy, compared with nonoperative therapy. Although the significant reduction in the failure rate was demonstrated with meta-analytic techniques, prospective, randomized trials should be performed to identify the optimal therapy for each clinical stage of empyema.

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## WE'RE FAILING

"To be permitted to read the rest of this column, you must first answer the following question correctly:

$\int (x - 1)^2\, dx$ is equal to

a) $2(x - 1) + c$
b) $\frac{1}{2}(x - 1)^2 + c$
c) $\frac{1}{3}(x - 1)^3 + c$
d) $\frac{1}{3}(x^3 - 1) + c$
e) $\frac{(x - 1)^3}{x} + c$

Go on, try it. After all, 83 percent of Japanese high school seniors got it right (though only 30 percent of American seniors). The correct answer is (c). If you answered incorrectly, though, keep reading—think of it as a social promotion. . . . Mr. Subbakrishna, a management consultant specializing in technology, notes that in his native Bangalore, children learn algebra in elementary school. All in all, he says, the average upper-middle-class child in Bangalore finishes elementary school with a better grounding in math and science than the average kid in the U.S. . . . I saw the same thing when I lived in China and interviewed college applicants there. The SAT wasn't offered in China, so Chinese high school students took the Graduate Record Examinations—intended for would-be graduate students—and many still scored in the 99th percentile in math. The latest international survey, called Trends in International Mathematics and Science Study, found that the best-performing eighth graders were, in order, from Singapore, South Korea, Taiwan, Hong Kong, Japan, Belgium and the Netherlands. The U.S. ranked 19th, just after Latvia. (India and China weren't surveyed.)"

Kristof ND. *New York Times*. February 14, 2005

Noted by JFL, MD

# Primary Operative Versus Nonoperative Therapy for Pediatric Empyema: A Meta-analysis

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