**Supplemental Material for 2026 Clinical Practice Guideline Update by the Infectious Diseases Society of America and the Pediatric Infectious Diseases Society on the Management of Community-Acquired Pneumonia in Infants and Children Older than 3 Months of Age: The Use of tPA and DNase or tPA Alone for Fibrinolysis**

***CONTENTS***

## CLINICAL PRACTICE GUIDELINE DEVELOPMENT PROCESS

### Guideline Panel Composition

The chairs of the guideline panel were selected by the leadership of IDSA. Twelve additional panelists comprised of the full panel. The panel included clinicians with expertise in infectious diseases, pediatric infectious diseases, and emergency medicine. Panelists were diverse in gender, geographic distribution, and years of clinical experience. Guideline methodologists oversaw all methodological aspects of the guideline development and identified and summarized scientific evidence for each clinical question. IDSA staff oversaw all administrative and logistic issues related to the guideline panel.

### Conflicts of Interest

All members of the expert panel complied with the IDSA policy on conflict of interest (COI), which requires disclosure of any financial, intellectual, or other interest that might be construed as constituting an actual, potential, or apparent conflict. Evaluation of such relationships as potential conflicts of interest was determined by a review process which included assessment by the Standards and Practice Guideline Subcommittee (SPGS) Chair, the SPGS liaison to the Guideline panel and the Board of Directors liaison to the SPGS, and if necessary, the Conflict of Interests Task Force of the Board. This assessment of disclosed relationships for possible COI was based on the relative weight of the financial relationship (i.e., monetary amount) and the relevance of the relationship (i.e., the degree to which an independent observer might reasonably interpret an association as related to the topic or recommendation of consideration). The reader of these guidelines should be mindful of this when the list of disclosures is reviewed. See the Notes section at the end of this guideline for the disclosures reported to IDSA.

### Practice Recommendations

Clinical Practice Guidelines are statements that include recommendations intended to optimize patient care by assisting practitioners and patients in making shared decisions about appropriate health care for specific clinical circumstances. These are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options [IOM 2011]. The "IDSA Handbook on Clinical Practice Guideline Development" provides more detailed information on the processes followed throughout the development of this guideline [IDSA CPG Handbook].

### GRADE Approach for Developing Clinical Practice Guidelines

The GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach for the assessment of the certainty of evidence and strength of recommendation was followed. For certainty of evidence of each critical and important outcome, risk of bias, indirectness, inconsistency, and imprecision were considered, along with publication bias and other special considerations according to GRADE (see Figure 1). (Guyatt 2008, Schunemann 2020) Risk of bias for non-randomized studies was assessed by the Newcastle Ottawa scale. This information is reported in evidence profiles developed using the GRADEpro Guideline Development Tool. Based on certainties of evidence for critical outcomes, a final judgment of confidence in the evidence was made for each recommendation.

The Evidence to Decision framework was used to translate evidence of summaries into practice recommendations. All recommendations are labeled as "strong" or "conditional" according to an evaluation of the certainty of evidence, the balance between benefits and harms, patients' values and preferences, resources/cost, and other factors such as acceptability, feasibility, and equity. Nonsystematic literature searches were used to inform these evaluations as needed. "The panel

recommends" indicates a strong recommendation, and "the panel suggests" indicates a conditional recommendation. Figure 1 provides the suggested interpretation of strong and conditional recommendations for patients, clinicians, and healthcare policymakers. Where there were knowledge gaps, the panel opted to provide limited clinical guidance for reasonable approaches, rather than no guidance at all, and these statements are specifically labeled as knowledge gaps.

### Approval Process

Feedback was obtained from two IDSA reviewers, three selected external peer reviewers, and the American Academy of Pediatrics (AAP). The IDSA Standards and Practice Guidelines Subcommittee (SPGS) and Board of Directors reviewed and approved the guideline prior to publication, along with any endorsing societies with the Pediatric Infectious Diseases Society (PIDS).

### Process for Updating

IDSA guidelines are regularly reviewed for currency. The need for updates to the guideline is determined by a scan of current literature and the likelihood that any new data would impact the recommendations. Any changes to the guideline will be submitted for review and approval to the appropriate Committees and Board of IDSA.

## SYSTEMATIC REVIEW PROCESS

### Clinical Question

The clinical question was formatted according to the PICO style: Patient/Population (P), Intervention (I), Comparator/Control (C), Outcome (O). For each PICO question, outcomes of interest were identified a priori and rated as critical, important, or not important, according to their relative importance for decision-making.

### Eligibility Criteria

Inclusion criteria:

- *Patient population*- Children with parapneumonic effusion requiring fibrinolytic therapy
- *Intervention* – tPA and DNase
- *Comparator*- tPA alone
- *Outcomes*- Need for further intervention, length of stay, recurrence, cost, morbidity
- *Study design*- Randomized controlled trials (RCTs) with no date limit, observational studies

Exclusion criteria:

- *Patient population*- International populations in resource limited settings
- *Comparator*- No comparator
- *Study design*- case reports

### Literature Search Methods

A medical librarian (EG) designed the literature searches for Medline via PubMed, Embase, and Cochrane Library, including appropriate MeSH terms, where applicable. Searches were limited to studies published in English. The initial formal literature searches were performed August 2019, and updated literature searches were conducted in October 2022 and July 2024. To supplement the electronic searches, reference lists of related articles and guidelines were reviewed for relevance.

### Study Selection

Titles and abstracts were screened in duplicate, and all potentially relevant citations were reviewed in full text by two panelists (SS and KA). Covidence was used to facilitate screening (Covidence

Systematic Review Software). Predefined inclusion and exclusion criteria tailored to meet the specific population, intervention, and comparator of each question were applied during the screening process. Abstracts and conference proceedings, letters to the editor, editorials, and review articles were excluded. The steps of the literature selection process were supervised and reviewed by a guideline methodologist for the final selection of the relevant articles. Details of this selection process are reported via PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagrams.

**Data Extraction**

A guideline methodologist in conjunction with panelists extracted the data for each pre-determined patient-important outcome.

**Assessment of Risk of Bias**

We assessed the risk of bias of individual studies using the Cochrane Risk of Bias tool (Higgins 2011).

**Data synthesis**

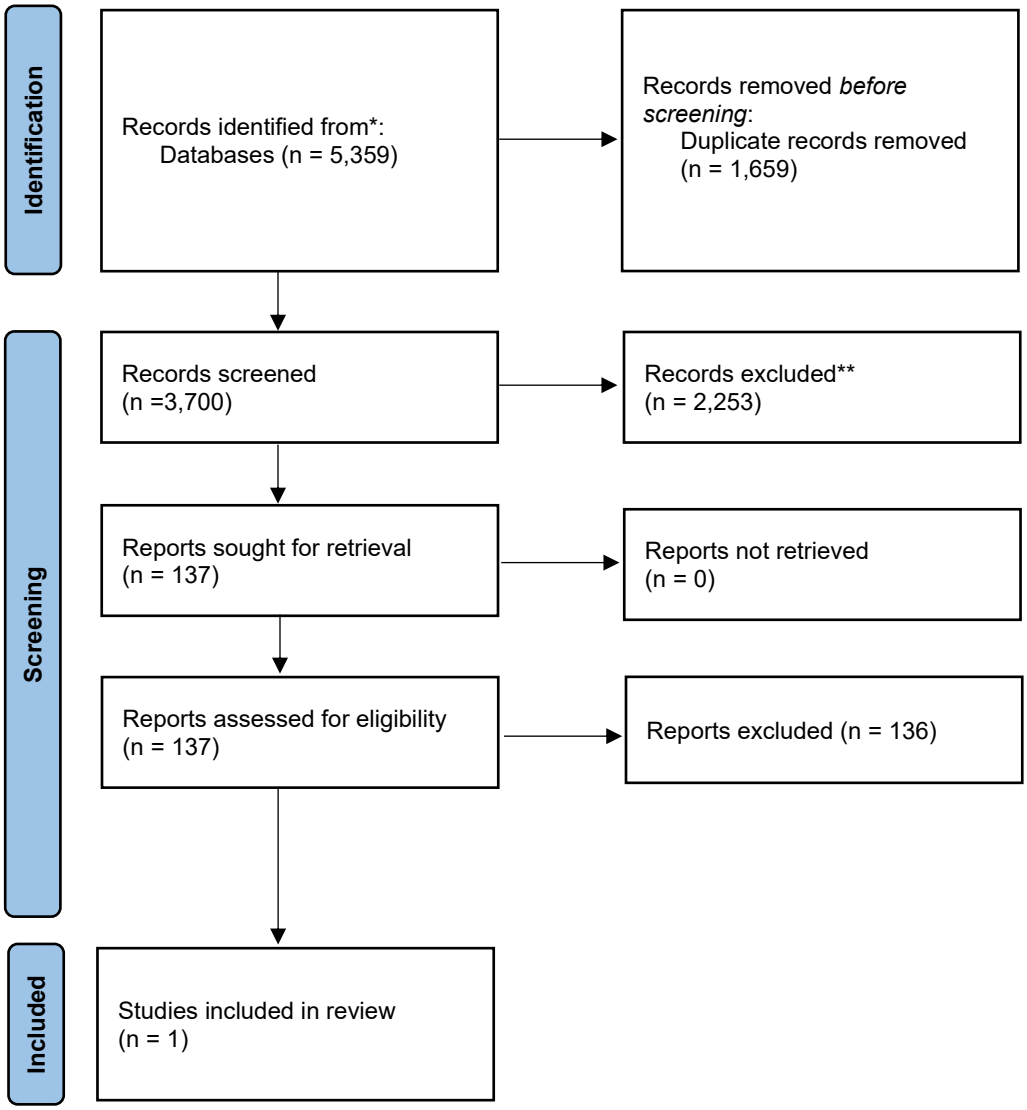
A guideline methodologist in conjunction with panelists extracted the data for each pre-determined patient-important outcome. Where applicable, data were pooled using a random-effects model (fixed effects model for pooling of rates) using RevMan [RevMan].

**Assessment of the Certainty of Evidence**

We assessed the certainty of evidence at the outcome level using the GRADE approach (Schünemann 2013). We followed the guidance developed by the GRADE working group to communicate the findings of the systematic review (Santesso 2020).

## SYSTEMATIC REVIEW RESULTS

### Results of the Search



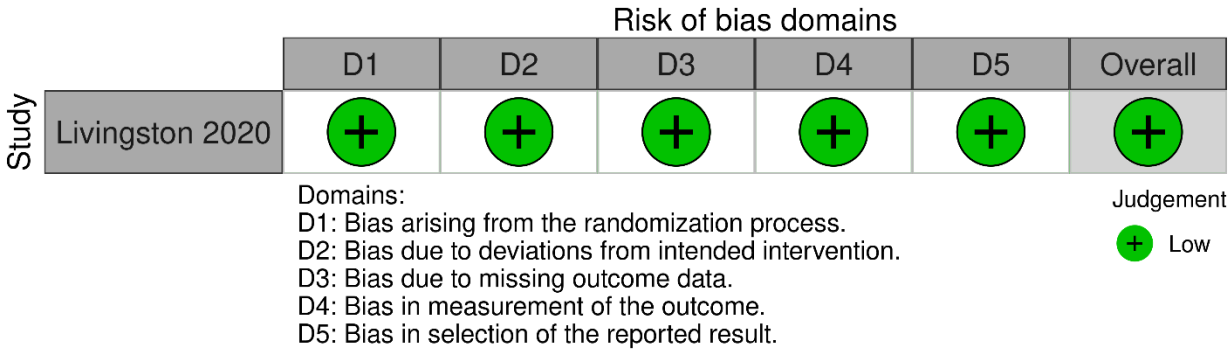

### Characteristics of Included Studies

| Author | Location | Study Design | Study Population | Number of Patients, age, | Intervention Description | Comparator Description |
|---|---|---|---|---|---|---|
| **Livingston 2020** | USA | RCT | Children 6m-18yrs with pleural empyema referred for pleural drainage; evidence of pleural effusion on US | N=97; median age 52m (IQR 36-66m) | tPA and DNase (n=49) | tPA and Placebo (n=48) |

## Evidence Tables

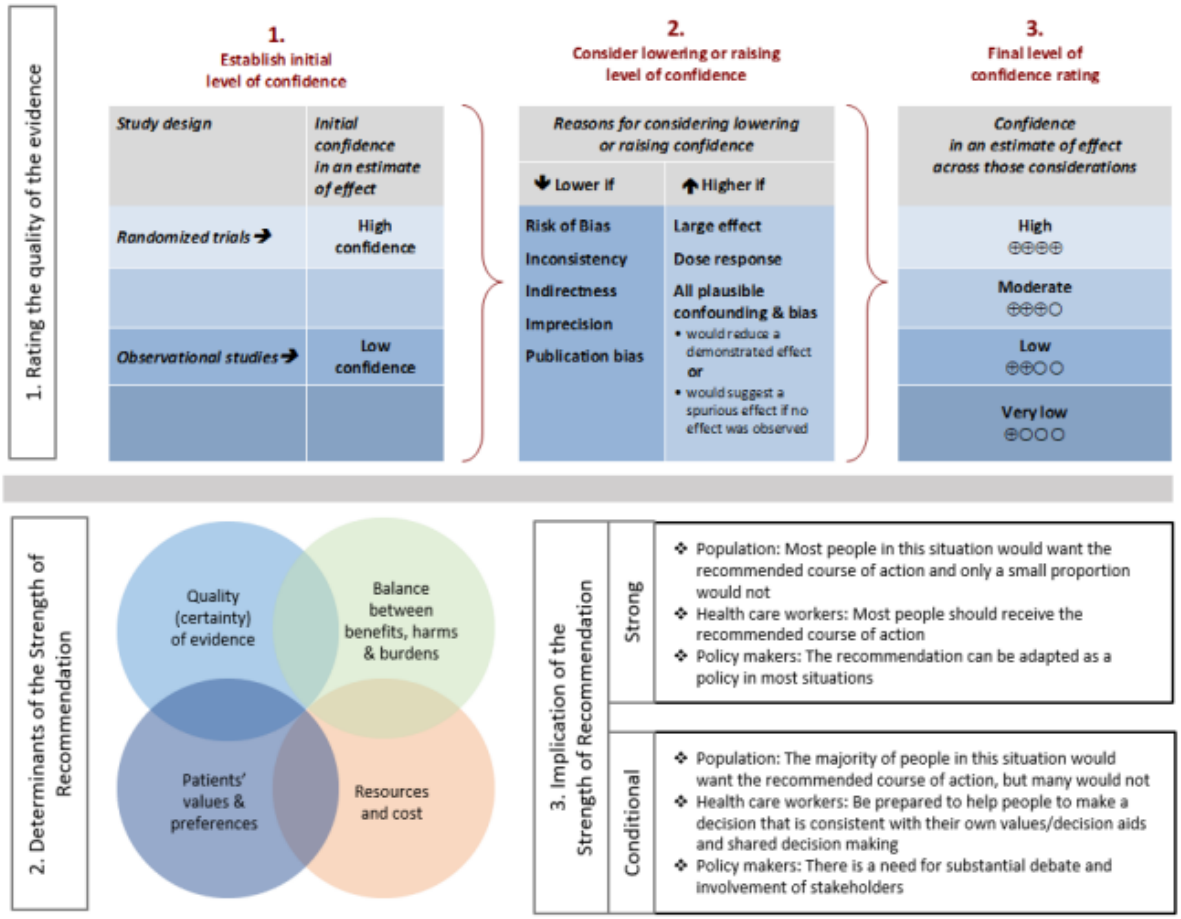
| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | tPA plus DNase | tPA alone | Relative (95% CI) | Absolute (95% CI) | | |
| **Post-intervention Length of Stay** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | very serious[a] | none | 49 | 48 | - | MD **0.1 days lower** (2 lower to 2.1 higher) | ⨁⨁◯◯ Low[a] | CRITICAL |
| **Additional Drainage Procedures** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | very serious[a] | none | 4/49 (8.2%) | 2/48 (4.2%) | **RR 1.96** (0.38 to 10.20) | **40 more per 1,000** (from 26 fewer to 383 more) | ⨁⨁◯◯ Low[a] | CRITICAL |
| **Any Adverse Event** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | very serious[a] | none | 12/49 (24.5%) | 14/48 (29.2%) | **RR 0.84** (0.43 to 1.63) | **47 fewer per 1,000** (from 166 fewer to 184 more) | ⨁⨁◯◯ Low[a] | CRITICAL |

**Risk of Bias Assessment in Included Studies**



## Other Tables and Figures

**Supplementary Figure 1.** Approach and implication to rating the certainty of evidence and strength of recommendations following the GRADE approach *(unrestricted use of figure granted by the US. GRADE network)*



## Search Strategies

### *PubMed (NLM)*

("Fibrinolytic Agents" [Pharmacological Action] OR "Fibrinolytic Agents"[Mesh] OR "Tissue Plasminogen Activator"[Mesh] OR "Streptokinase"[Mesh] OR "Urokinase-Type Plasminogen Activator"[Mesh] OR "Thrombolytic Therapy"[Mesh] OR "T Plasminogen Activator"[tiab] OR "Tisokinase"[tiab] OR "Tissue Activator D 44"[tiab] OR "tissue plasminogen activator"[tiab] OR "Tissue Type Plasminogen Activator"[tiab] OR "tPA"[tiab] OR "U-PA"[tiab] OR "Urokinase"[tiab] OR "Debridement"[Mesh] OR debrid*[tiab] OR "Chest Tubes"[Mesh] OR "chest tube"[tiab] OR "chest tubes"[tiab] OR "chest drain"[tiab] OR "chest drains"[tiab] OR "pleural tube"[tiab] OR "pleural tubes"[tiab] OR "pleural drain"[tiab] OR "pleural drains"[tiab] OR "small bore"[tiab] OR "large bore"[tiab] OR "Tube thoracostomy"[tiab] OR "<12Fr"[tiab] OR ">14fr" [tiab]) AND ("Empyema, Pleural"[Mesh] OR "Pleural Effusion"[Mesh] OR "pleural effusion"[tiab] OR "pleural effusions"[tiab] OR "pleura effusion"[tiab] OR "pleura effusions"[tiab] OR "parapneumonic effusion"[tiab] OR "parapneumonic effusions"[tiab] OR "pleural suppuration"[tiab] OR "lung effusion"[tiab] OR "lung effusions"[tiab] OR "empyema"[tiab])) AND (("Adolescent"[Mesh] OR "Child"[Mesh] OR "Child, Preschool"[Mesh] OR "Infant"[Mesh] OR "adolescence"[tiab] OR "adolescent"[tiab] OR "adolescents"[tiab] OR "baby"[tiab] OR "babies"[tiab] OR "child"[tiab] OR "childhood"[tiab] OR "children"[tiab] OR "infant"[tiab] OR "infants"[tiab] OR "infancy"[tiab] OR "juvenile"[tiab] OR "paediatric"[tiab] OR "paediatrics"[tiab] OR "pediatric"[tiab] OR "pediatrics"[tiab] OR "preschool child" [tiab] OR preschool children"[tiab] OR "teen"[tiab] OR "teenager"[tiab] OR "teenagers"[tiab] OR "teens"[tiab] OR "toddler"[tiab] OR "toddlers"[tiab] OR "youth"[tiab] OR "youths"[tiab])

### *EMBASE*

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'teens':ti,ab OR 'toddler':ti,ab OR 'toddlers':ti,ab OR 'youth':ti,ab OR 'youths':ti,ab)

***Cochrane (Wiley)***

([mh "Empyema, Pleural"] OR [mh "Pleural Effusion"] OR "pleural effusion":ti,ab OR "pleural effusions":ti,ab OR "pleura effusion":ti,ab OR "pleura effusions":ti,ab OR "parapneumonic effusion":ti,ab OR "parapneumonic effusions":ti,ab OR "pleural suppuration":ti,ab OR "lung effusion":ti,ab OR "lung effusions":ti,ab OR "empyema":ti,ab) AND ([mh “chest tubes”] OR "chest tube":ti,ab OR "chest tubes":ti,ab OR "chest drain":ti,ab OR "chest drains":ti,ab OR "pleural tube":ti,ab OR "pleural tubes":ti,ab OR "pleural drain":ti,ab OR "pleural drains":ti,ab OR "small bore":ti,ab OR "large bore":ti,ab OR "Tube thoracostomy":ti,ab OR "<12Fr":ti,ab OR ">14fr":ti,ab OR [mh "Fibrinolytic Agents"] OR [mh "Tissue Plasminogen Activator"] OR [mh "Streptokinase"] OR [mh "Urokinase-Type Plasminogen Activator"] OR [mh "Thrombolytic Therapy"] OR "T Plasminogen Activator":ti,ab OR "Tisokinase":ti,ab OR "Tissue Activator D 44":ti,ab OR "tissue plasminogen activator":ti,ab OR "Tissue Type Plasminogen Activator":ti,ab OR "tPA":ti,ab OR "U-PA":ti,ab OR "Urokinase":ti,ab OR [mh "Debridement"] OR debrid*:ti,ab) AND ([mh "Adolescent"] OR [mh "Child"] OR [mh "Child, Preschool"] OR [mh "Infant"] OR "adolescence" OR "adolescent" OR "adolescents" OR "baby" OR "babies" OR "child" OR "childhood" OR "children" OR "infant" OR "infants" OR "infancy" OR "juvenile" OR "paediatric" OR "paediatrics" OR "pediatric" OR "pediatrics" OR "preschool child" OR "preschool children" OR "teen" OR "teenager" OR "teenagers" OR "teens" OR "toddler" OR "toddlers" OR "youth" OR "youths")

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GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University and Evidence Prime, 2024. Available from gradepro.org.

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