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

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ABSTRACT.

This paper is part of a larger clinical practice guideline on the diagnosis and management of parapneumonic effusion and empyema in children, developed by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. In this report, the panel provides recommendations for intrapleural fibrinolysis with tissue plasminogen activator (tPA) alone over tPA and dornase alfa (DNase) in children (3 months to 18 years) with complicated parapneumonic effusion and empyema. The panel's recommendations are based upon evidence derived from systematic literature reviews and adhere to a standardized methodology for rating the certainty of evidence and strength of recommendation according to the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach.

Key words. Parapneumonic empyema, tissue plasminogen activator (tPA), dornase alfa (DNase)

In children (3 months to 18 years) with parapneumonic empyema, should tPA and DNase or tPA alone be used for chemical debridement?

Recommendation: In children (3 months to 18 years of age) with pneumonia-associated empyema, the panel suggests administering tPA alone over tPA and DNase *(conditional recommendation, low certainty of evidence)*

*A **strong** recommendation means most informed people would choose the recommended course of action and* only a small proportion *would not.*
*A **conditional** recommendation means the majority of informed people would choose the suggested course of action but* many *would not.*

INTRODUCTION

Parapneumonic effusion refers to a purulent collection in the pleural space with or without infection. As part of the management of complicated pneumonia, pleural fluid drainage with a thoracostomy tube and intrapleural fibrinolysis hastens clinical recovery.

This paper is part of a larger clinical practice guideline on the diagnosis and management of parapneumonic effusion and empyema in children, developed by the Pediatric Infectious Disease Society (PIDS) and the Infectious Diseases Society of America (IDSA), and has been endorsed by the Pediatric Infectious Diseases Society (PIDS).

In this paper, the guideline panel provides recommendations for the use of fibrinolysis in the management of complicated parapneumonic effusion and empyema. These recommendations replace previous statements in the last iteration of this guideline [1, 2]. These recommendations are intended for use by healthcare professionals who care for children with parapneumonic effusion and empyema.

METHODS

The panel's recommendation is based on evidence derived from a comprehensive systematic literature review and adhere to a standardized methodology for rating the certainty of evidence and strength of recommendation according to the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach [3]. The 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. More details about the systematic review and guideline development processes are presented in the Supplementary Material.

A comprehensive literature search (through July 2024) was conducted as part of a systematic review. Key eligibility criteria at both the topic and clinical question levels guided the search and selection of studies for inclusion. For this question, the panel considered patients 3 months to 18 years of age with complicated parapneumonic effusion defined as empyema, undergoing pleural fluid drainage and interpleural fibrinolytics. Studies evaluating and comparing different fibrinolytics were included. Studies with adult populations were excluded, as well as international populations in resource-limited areas. Randomized controlled trials and observational studies were screened for inclusion.

Included studies were assessed for risk of bias using the Cochrane Risk of Bias tool [4]. Included studies underwent critical appraisal according to the GRADE approach. An assessment of the benefits and harms of care options informed the recommendation(s) [3]. Details of the systematic review and guideline development processes are available in the Supplementary material.

SUMMARY OF EVIDENCE

A comprehensive literature search identified a single randomized controlled trial (RCT) that met the panel's inclusion criteria [5]. In this study, a total of 97 children with parapneumonic empyemas requiring pleural drainage were randomized to receive either tPA and placebo or tPA followed by DNase. Treatment with tPA and DNase was not associated with decreased hospital length of stay compared with tPA and placebo (mean [SD] length of stay, 9.0 [4.9] vs 9.1 [5.3] days; mean difference [MD] -0.1 days; 95%CI, −2.0 to 2.1; p=0.96). Similarly, no significant differences were observed for the need for additional intervention, such as repeat pleural drainage procedures (8% in the tPA plus DNase vs. 4% in the tPA plus placebo group; MD 4.0%; 95% CI -5.5 to 13.5; p=0.41). There were a similar number of adverse events across both groups (tPA and DNase, 24% vs tPA alone, 29%; p=0.64), and no deaths were reported in either group.

The overall certainty of evidence for the reported outcomes is low because of imprecision due to the small sample size and wide confidence intervals. Refer to the Supplementary Material for the GRADE Evidence Profiles which detail the exact judgments affecting certainty of evidence for each outcome.

RATIONALE FOR RECOMMENDATION(S)

While the single included RCT demonstrated similar outcomes when using tPA compared to tPA plus DNase in children with parapneumonic empyema, the panel conditionally suggests giving tPA alone over tPA and DNase. The panel discussed the cost of DNase is typically higher and it is not approved for intrapleural use in the United States, making the feasibility of its implementation difficult. Further, the addition of DNase requires a second delivery of medication. Given that the RCT evidence showed no advantage to for the addition of DNase to tPA compared with saline placebo, use of this additional medication is not currently justified.

IMPLEMENTATION CONSIDERATIONS

Tissue plasminogen activator is readily available in any market and hospital, and there should not be local implementation barriers. A clinical setting with the ability to insert a thoracostomy tube should be able to administer tPA into the pleural space as part of management for parapneumonic effusion and empyema. The panel carefully considered a potential subgroup effect across patients from different age groups i.e. less than 5 years; 5 to 13 years; 14 to 18 years, and across patient strata with pleural empyema. Nevertheless, the evidence from the existing literature did not allow us to make recommendations for different patient categories. Therefore, this recommendation applies to patients between 3 months to 18 years of age with either parapneumonic effusion or empyema.

RESEARCH NEEDS

The panel suggests the use of tPA alone (versus tPA plus DNase) as the preferred therapy for children (3 months to 18 years) with complicated parapneumonic effusion and empyema. Further research with fibrinolysis protocols may be valuable to test the protocols' effectiveness. There are no data on the effectiveness and safety of the management strategies on different subgroups. Therefore, more research is needed in this area.

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Samir S. Shah is chair of the pediatric CAP guideline panel. Mark Neuman is the vice-chair of the panel. Shawn St Peter and Krow Ampofo served as clinical leads for the questions addressed in this manuscript. Remaining panelists assisted with conception and design of the analysis, interpretation of data, drafting and revising the recommendations and manuscript, and final approval of the recommendations and manuscript to be published. Nigar Sekercioglu and Sheena Patel, methodologists, were responsible for general project management, designing and performing the systematic review, and leading the panel according to the GRADE process.

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relationship in which a spouse served as a consultant for echocardiography study interpretation for the Midwest Cardiovascular Research and Education (MCORE) Foundation. **D.J.W.** received research funding from AHRQ and NIH for work related to the Seattle-based Pediatric Health Information Partnership (P-HIP) initiative aimed at improving pediatric mental health care; serves on the Executive Council for the Pediatric Research in Inpatient Setting (PRIS) Network; serves on the Editorial Board for the Journal of Hospital Medicine; receives research funding from AHRQ and NIH. **S.S.S.** served in editorial roles with JAMA Pediatrics for the American Medical Association; served as senior deputy editor and then editor-in-chief for the Journal of Hospital Medicine for the Society of Hospital Medicine; served as associate editor for the Journal of the Pediatric Infectious Diseases Society; served as a Committee on Infectious Diseases member for the American Academy of Pediatrics; served as vice-chair for Pediatric Research in Inpatient Settings; received honoraria from the Society of Hospital Medicine; received research funding from NIAID, NHLBI, PCORI, and the Ohio Department of Public Health. **M.N.** served as associate editor for Pediatrics for the American Academy of Pediatrics; received research grants from Harvard University; serves as Co-Editor-in-Chief of Pediatric Emergency Care; receives honoraria from Wolters Kluwer for editorial roles with UpToDate and Pediatric Emergency Care; provides medical expert consultation, including medical record review and expert testimony in legal cases for law firms on issues not related to pneumonia.

The following panelists have reported relationships with the indicated companies since 2018, when guideline development began; these relationships are **related to the topic of community-acquired pneumonia (CAP)**. **K.K.A.** served in advisory roles involving patient enrollment for clinical trials with Johnson & Johnson and Merck related to lumicitabine, tedizolid, ceftolozane/tazobactam, and bezlotoxumab (all such relationships are no longer active). **D.L.P.** served on a data safety monitoring board for Pfizer for a trial related to azithromycin; received honoraria from Medscape related to an educational podcast (relationship ended in 2024); owns intellectual property related to educational materials for Elsevier; receives other remuneration from the AMA. **D.J.W.** received research funding from NIH/NIAID for work related to Vanderbilt/ICE-CAP/R01AI125642 and Vanderbilt/VTEU/HHSN272201300023I, CDC for work related to Vanderbilt/NVSN/U01IP001063 and AHRQ for work related to R01HS029331, the Reducing Overuse of Antibiotics with Decision Support (ROADS) study aimed at testing the safety and effectiveness of clinical decision support to promote antibiotic stewardship in lower respiratory tract infections in children; received in-kind research support from bioMérieux for procalcitonin assays related to CAP decision-making (this relationship is no longer active); reported a family relationship in which a spouse is employed by Pfizer and the funds are paid directly to them. **M.N.** served as a member of the Guideline Development Group of the World Health Organization for the Diagnosis and Management of Pneumonia and Diarrhea in Children. **All other authors reported no disclosures**.

Additional Information: More detailed information on the analysis and development of recommendations is available in the Supplementary file.

REFERENCES

1. Bradley JS, Byington CL, Shah SS, et al. Executive summary: the management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis **2011**; 53(7): 617-30.
2. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis **2011**; 53(7): e25-76.
3. Guyatt GH, Oxman Ad Fau - Vist GE, Vist Ge Fau - Kunz R, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. **2008**; (1756-1833 (Electronic)).
4. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ **2011**; 343.
5. Livingston MH, Mahant S, Connolly B, et al. Effectiveness of Intrapleural Tissue Plasminogen Activator and Dornase Alfa vs Tissue Plasminogen Activator Alone in Children with Pleural Empyema: A Randomized Clinical Trial. JAMA Pediatr **2020**; 174(4): 332-40.