



Evidence-Based Guideline on Prioritized Issues for the Management of Empyema Thoracis in Children

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Abstract

Justification The lack of clarity in the management of pediatric empyema thoracis necessitates evidence-based guidance.

Objective To develop an evidence-based guideline on high-priority issues in pediatric empyema management (laboratory investigations, antibiotic therapy, intrapleural fibrinolytic therapy, surgical intervention, and follow-up).

Process The guideline was developed using contemporary methodology, viz. establishing a Steering Group; setting up an Evidence-Based Guideline Development Group (EBGDG); collating formal declarations of interest and managing conflicts; identifying and prioritizing questions; evidence synthesis; critical appraisal using GRADE methodology; translating evidence to recommendation statements; external peer review; and finalization of the guideline document.

Recommendations The dominant pathogen causing empyema in Indian children is *Staphylococcus aureus*, followed by *Streptococcus pneumoniae*. Therefore, the empirical antibiotics (pending culture reports) should preferably be the combination of Cloxacillin and Ceftriaxone (conditional recommendation, very low certainty of evidence). On the issue of intrapleural fibrinolytic therapy (IPFT) vs. no IPFT as the initial modality, pediatricians could use either option (in addition to oxygen, appropriate antibiotics, and effective pleural pus drainage) as the limited evidence did not show significant differences for critical outcomes (conditional recommendation, very low certainty of evidence). However, IPFT is recommended as the initial modality of therapy compared to Video-Assisted Thoracoscopic Surgery (VATS), on account of comparable efficacy, moderate savings, enhanced equity, stakeholder acceptability, and feasibility in diverse settings (conditional recommendation, very low certainty of evidence). The EBGDG does not recommend any particular intrapleural fibrinolytic agent over another due to a lack of comparative evidence (conditional recommendation, no evidence). The superiority of early initiation of IPFT (i.e. as the initial management, or at presentation), compared to late(r) instillation is not established in the absence of any evidence (conditional recommendation, no evidence). No recommendation can be made regarding the use of initial intrapleural fibrinolytic therapy (IPFT) (i.e., at or close to confirmation of empyema) versus IPFT after failure of intercostal chest drain (ICD) alone because of the absence of evidence (conditional recommendation, no evidence). Antibiotic therapy for ≤4 weeks is not suggested in preference to therapy for >4 weeks, despite the absence of direct evidence, owing to greater clinical experience with the latter, as well as its acceptability and feasibility (conditional recommendation, no evidence). Routine use of microbiologic molecular methods in preference to conventional culture techniques is not suggested, on account of greater specificity and lower cost of culture (conditional recommendation, very low certainty of evidence). Routine use of CT scan in preference to ultrasonography is not suggested for the management of

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children with empyema (conditional recommendation, very low evidence certainty). No clinical, radiological, microbiological, biomarker, or pleural fluid characteristics, either individually or in combination, were identified as predictors of failure of medical management (conditional recommendation, very low certainty of evidence). For each evidence-based recommendation, detailed justification, implementation considerations, and research priorities are outlined.

Conclusion This evidence-based guideline, developed using robust methodology, offers practical guidance for the management of empyema thoracis in children. This is expected to enhance the quality and standardization of care.

Keywords Empyema thoracis · Evidence-based guidelines · GRADE · Intrapleural fibrinolytic · Pediatric empyema · Video-assisted thoracoscopic surgery

Introduction

Community-acquired pneumonia (CAP) in children is a major concern globally [1]. The burden of disease is particularly high in India [2, 3]. Some children with pneumonia develop parapneumonic effusion, which may become infected, leading to pus formation, referred to as empyema thoracis [4–6]. Childhood empyema has several adverse consequences for affected individuals [7]. The effective management of empyema involves appropriate antibiotic therapy, efficient drainage of pleural pus, and supportive care [8]. However, there are finer details within these three pillars, such as the choice and duration of antibiotics, optimal modalities for pus drainage, need for intrapleural fibrinolytic therapy (IPFT), timing, nature, and regimen(s) of fibrinolytic therapy, considerations for surgical management, appropriate imaging modalities, optimal use of laboratory tests, monitoring during management, and follow-up protocols. A nationwide survey of pediatricians identified wide variations in clinical practice across all these aspects of clinical management [9]. This necessitates urgent guidance for physicians managing pediatric empyema thoracis.

Need for Guidelines

There are a limited number of guidelines issued by national and international agencies, which have attempted to address empyema management. However, the two Indian documents [10, 11] are not evidence-based guidelines and lack methodological rigor. In contrast, whilst some of the international guidelines have better methodology [12–18], they also do not substantially address the issues of interest identified in the national survey [9]. Further, there are challenges with the transferability and applicability of recommendations from developed healthcare settings to the Indian context.

Objectives

These considerations prompted the development of an evidence-based guideline and management recommendations

for pediatricians in India (and other developing countries) for the effective, efficient, and economical management of empyema thoracis in children.

Process

The methodology for developing this evidence-based guideline was aligned with the principles outlined in the World Health Organization (WHO) handbook for evidence-based guidelines [19]. Broadly, it involved establishing a Steering Group that defined the scope and purpose of the guideline; setting up an Evidence-Based Guideline Development Group (EBGDG); collating formal declarations of interest and managing conflicts; identifying and prioritizing questions to be addressed; evidence synthesis addressing the questions; critical appraisal of the evidence using GRADE methodology; translating evidence into actionable recommendation statements; external peer review; and finalizing the guideline document for dissemination, implementation, and updating. The detailed methodology is described in this issue of the journal [20].

Recommendations

The EBGDG identified 11 priority questions requiring evidence-based guidance. These questions, outlined in the PICOTS (Population, Intervention/Exposure, Comparison, Outcome, Timeframe, Setting) format, are presented in Web File 1. The evidence syntheses [21–31] addressing these questions are also presented. The recommendation for each question, with a summary of the justification, subgroup considerations, implementation considerations, monitoring and evaluation during implementation, and research priorities, is presented herein.

Question 1: What are the efficacy, safety, and cost of IPFT as the initial modality vs. no IPFT in children with empyema?



Recommendation

In addition to standard care (viz. oxygen if required, appropriate antibiotic therapy, and intercostal drainage, ICD), we suggest that clinicians may use IPFT or manage without IPFT as the initial modality in children with empyema (conditional recommendation, very low certainty of evidence).

Justification

The body of evidence [21] was limited to three RCTs [32–34]. All three reported “failure of therapy”; the pooled OR (95%CI) was 0.14 (0.02, 1.12), $I^2 = 50\%$, with random effects meta-analysis and 0.15 (95% CI 0.04, 0.50, $I^2 = 50\%$) with the fixed-effect model; 146 participants, very low certainty. None of the trials reported the “need for open thoracotomy”. Two RCTs [32, 34] described some clinical outcomes at three months of discharge, but these were very limited and insufficient to make a recommendation favoring either option.

Only one RCT [32] reported a few adverse events, and there was no difference between the intervention and comparison. The certainty of evidence was very low. There was no data comparing costs or cost-effectiveness of the two modalities.

In contrast, indirect evidence from observational studies [35, 36] and a Cochrane review in adults [37] showed some benefits with IPFT, without serious adverse events with IPFT.

Subgroup Considerations

There was no evidence to recommend in favor of, or against, IPFT in any subgroup of children with empyema.

Implementation Considerations

End-users should note that the question was focused on IPFT (vs. no IPFT) as the *initial* treatment modality. Further, the recommendation offered is for children with confirmed empyema, which is not synonymous with parapneumonic effusion. Although IPFT is feasible, it should be administered with the required skills for its installation and monitoring. The usual protocol is to instil it with normal saline, with a two-hour dwell time, during which the child’s posture should be sequentially changed [38]. Thereafter, the fluid is allowed to drain, and the volume is carefully recorded until the next dose. The conventional usage is over three days, with once-daily dosing for streptokinase or tissue plasminogen activator, and twice-daily dosing for urokinase. Clinicians should carefully consider factors such as cost, available resources,

and patient and caregiver values while choosing between IPFT and no IPFT.

Monitoring and Evaluation

Clinical monitoring includes vital signs, clinical symptoms and signs, fluid drainage, and (if/when required) radiological imaging. Clinicians should also be aware of the clinical signs of “treatment failure” with either approach and avoid delays in escalating therapy if required. Those using IPFT should be aware of the known side effects, monitor for them, and counsel patients appropriately.

Physicians using either modality should maintain meticulous records, as these can contribute to indirect evidence of efficacy, safety, patient preferences, feasibility, and cost.

Research Priorities

Well-designed multicentric trials are required to determine the efficacy and safety of IPFT versus no IPFT in India.

Question 2: What are the efficacy, safety, and cost of IPFT versus video-assisted thoracoscopic surgery (VATS) as the initial treatment modality in children with empyema?

Recommendation

In situations where an additional therapy apart from standard care (viz. oxygen if required, appropriate antibiotic therapy, and ICD) is considered, we recommend the intervention (IPFT) as the initial modality of therapy over VATS, as it showed comparable efficacy, but is associated with moderate savings, likely to enhance equity, probably acceptable to all stakeholders, and likely to be feasible in diverse settings (conditional recommendation, very low certainty of evidence).

Justification

The body of evidence [22] comprised five RCTs [39–43]. The pooled OR (95% CI) for (i) failure of therapy was 1.01 (0.46, 2.21), $I^2 = 9\%$, 4 trials, 235 participants, very low certainty; (ii) need for open thoracotomy: OR 0.24 (0.06, 1.06), $I^2 = 0\%$, 3 trials, 199 participants, low certainty; and (iii) serious adverse events OR 0.67 (0.24, 1.90), $I^2 = 0\%$, 4 trials, 235 participants, low certainty. None of the trials reported clinical outcomes within 3 months of discharge. Length of stay and cost of therapy were reported in all five trials, but in variable formats, precluding meta-analysis. Four trials showed a higher cost with VATS than IPFT. The EBGDG expected moderate



savings with IPFT, as well as enhanced equity, greater acceptability, and feasibility.

Subgroup Considerations

There was no evidence to recommend in favor of or against the intervention in any subgroup of children with empyema.

Implementation Considerations

This recommendation is for children with confirmed empyema, which is not synonymous with parapneumonic effusion. Further, it focuses on IPFT vs. VATS as the *initial* treatment modality. IPFT is feasible in a wide range of clinical settings and does not require surgical expertise, unlike VATS. However, it should be administered with clinical skills for instillation and monitoring, as described in Question 1. In contrast, VATS may also offer certain advantages (e.g., removal of fibrinous material and lysis of adhesions under direct visualization), although it cannot be repeated as often as IPFT. Clinicians should consider factors such as cost, available resources, and patient and caregiver values when choosing between IPFT and VATS.

Monitoring and Evaluation

Clinical monitoring is exactly as described in Question 1.

Research Priorities

Well-designed multicentric trials are required to determine the long-term efficacy, safety, and cost-effectiveness of IPFT versus VATS in India.

Question 3: What are the comparative efficacy, safety, and cost of different intrapleural fibrinolytic agents used for the management of empyema in children?

Recommendation

We do not recommend any particular intrapleural fibrinolytic agent (streptokinase, urokinase, alteplase) over another due to the lack of comparative evidence on efficacy, safety, and cost. If physicians choose to use IPFT, they may use any of these agents based on clinical judgment and/or consideration of individual patient circumstances and/or the healthcare setting (conditional recommendation, no evidence).

Justification

There were no RCTs directly comparing the efficacy, safety, or cost of different intrapleural fibrinolytic agents

(streptokinase, urokinase, alteplase) in children with empyema [23]. In India, streptokinase is the least expensive, most widely available/accessible, and associated with extensive clinical experience over three decades. However, observational studies and clinical experience have shown that it may be associated with some side effects, notably fever and transient bleeding. Urokinase may offer a better safety profile and is comparably priced, but is less accessible in many Indian institutions. Alteplase is significantly more expensive, and there is limited experience with its use in India.

Subgroup Considerations

There was no evidence to recommend in favor of, or against, any particular intrapleural fibrinolytic agent in any subgroup of children with empyema.

Implementation Considerations

The choice of fibrinolytic agent may be influenced by local availability, cost, clinician familiarity, and institutional protocols. Clear communication with caregivers is essential to explain the rationale for the choice and the current lack of comparative evidence. Successful implementation also requires adequate training, monitoring, and follow-up facilities for IPFT.

Monitoring and Evaluation

Regular clinical monitoring is exactly as described in Question 1.

Research Priorities

Multicentric trials are required to compare the efficacy, safety, cost, and cost-effectiveness of various intrapleural fibrinolytic agents in children with empyema.

Question 4: In children with empyema, is early initiation of fibrinolytic therapy (i.e. as the initial management, or at presentation) superior to late(r) (r) instillation?

Recommendation

If physicians choose to use IPFT in addition to standard care, we do not offer a recommendation favoring either the intervention (early initiation, i.e., as the initial management, or at presentation) or the comparison (later instillation, i.e., after a trial of ICD alone for any duration >24 h) as there is no evidence supporting one approach over the other (conditional recommendation, no evidence).



Justification

No RCT was identified comparing early initiation of fibrinolytic therapy (i.e., at presentation or as initial management) versus late(r) instillation in children with empyema [24]. There was not even indirect evidence to guide considerations on efficacy, safety, cost, feasibility, acceptability, or equity.

Subgroup Considerations

There was no evidence to recommend in favor of or against either option in any subgroup of children with empyema.

Implementation Considerations

For clinicians preferring either option, these are exactly as described for Questions 1 to 3.

Monitoring and Evaluation

If clinicians use IPFT, regular clinical monitoring is exactly as described in Question 1.

Research Priorities

A well-designed trial is required to determine the efficacy and safety of early initiation (i.e. as the initial management, or at presentation), versus late instillation of fibrinolytic therapy in children with empyema.

Question 5: In children with empyema, how does initial IPFT, i.e., at or close to confirmation of empyema, compare to IPFT after failure of ICD alone?

Recommendation

If physicians choose to use IPFT in addition to standard care, we do not offer a recommendation favoring either the intervention (initial IPFT at or close to confirmation of empyema) over the comparison (IPFT after failure of ICD alone), as there is no evidence supporting one approach over the other (conditional recommendation, no evidence).

Justification

There were no randomized trials addressing the review question [25]. In the three RCTs [32–34] comparing IPFT vs. placebo, the timing of IPFT was not specified. Similarly, in the five RCTs comparing IPFT vs. VATS as the initial treatment modality [39–43], the timing of IPFT initiation was not clearly specified. Exploration of indirect evidence identified a few retrospective observational studies [44–53]

in patients with complicated parapneumonic effusion or empyema. These suggested that IPFT may be beneficial in 60–100% of patients not responding to ICD and antibiotics alone. However, these studies used IPFT even in parapneumonic effusion (rather than only empyema), had varying definitions of ICD failure, and different timings of IPFT administration. Many also lacked separate reporting of outcomes in empyema cases. The EBGDG did not find any studies reporting cost differences between early IPFT and delayed use after failure of ICD. While the cost of fibrinolytics may be similar regardless of timing, delaying their use may allow some children to recover without them, potentially saving resources. In contrast, for those requiring IPFT later, costs may increase due to a longer hospital stay. There was no evidence to guide considerations on feasibility, acceptability, and equity.

Subgroup Considerations

There was no evidence to recommend in favor of or against either option in any subgroup of children with empyema.

Implementation Considerations

In the absence of clear evidence favoring either option, clinical decisions should be guided by patient condition, resource availability, and physician experience. Some children with empyema may improve with ICD and antibiotics alone. Early use of IPFT may shorten hospital stay in selected cases, but may also expose some children to unnecessary intervention and associated adverse events. Delayed use after ICD failure may prolong hospitalization or increase the risk of complications. Therefore, local practice patterns, availability of fibrinolytic agents, and hospital infrastructure should inform decision-making until robust evidence becomes available.

Monitoring and Evaluation

In clinical settings where IPFT is used, monitoring should focus on systematically recording when IPFT is initiated (at diagnosis vs. after ICD failure), clinical outcomes (viz. time to clinical improvement, duration of hospitalization, need for surgical intervention), and adverse events related to therapy. This will help evaluate real-world effectiveness, inform ongoing clinical decisions, and contribute data for future research to strengthen the evidence base regarding optimal timing of IPFT in pediatric empyema.



Research Priorities

Well-designed trials are required, comparing initial IPFT (at or close to confirmation of empyema) vs. IPFT after failure of ICD alone. Subgroup analysis based on the timing in the intervention arm (immediate vs. not immediate but within 24 hours) and timing in the comparison arm (failure of ICD alone within 3 days vs. beyond 3 days) will be particularly useful.

Question 6: What is the microbial etiology of empyema in children?

Summary of Evidence

A total of 36 studies were included in the systematic review [26]. Seven Indian studies [54–60] in 562 children showed the pooled prevalence (95% CI) of organisms in pleural fluid as *Staphylococcus aureus* 51.0% (34.3, 67.7); *Streptococcus pneumoniae* 17.8% (0.6, 35.0); *Pseudomonas spp.* 11.0% (0.0, 23.0); and *Klebsiella spp.* 3.8% (0.4, 7.3). *Escherichia coli*, *Haemophilus influenzae*, *Enterococcus*, other microorganisms, and mixed microorganisms were prevalent in <1% of cases. In contrast, 22 studies with 1727 children from other countries reported pooled prevalence (95% CI) of *S. aureus* 35.3% (23.7, 47.0) and *S. pneumoniae* 36.1% (25.1, 47.1).

Among the 27 studies where *S. aureus* was identified, classification as methicillin-sensitive or resistant (MSSA or MRSA) was reported in only five. There was a widely varying prevalence of MRSA (among total *S. aureus* isolates), ranging from 15.5% to 100%. The data were too heterogeneous for pooling.

Four Indian studies with 296 children (having empyema) reported organisms in blood culture. Here also, the major organisms were *S. aureus* 30.3% (6.7, 53.8); *S. pneumoniae* 19.2% (0.0, 43.4); *Pseudomonas spp.* 9.2% (1.5, 16.9), and *Klebsiella spp.* 8.9% (0.7, 17.1). Other organisms contributed < 1% each. In contrast, 11 studies with 500 children from other countries identified *S. pneumoniae* as the dominant organism in 77.3% (61.1, 93.4), with *S. aureus* in only 2.6% (0.0, 8.0). Only two studies classified *S. aureus* as MSSA or MRSA in blood culture; the prevalence of MRSA (among total *S. aureus* isolates) ranged from 16.6% to 100%.

Only five studies [56, 61–64] reported antibiotic susceptibility patterns. The number of isolates tested against various antibiotics ranged from 1 to 31, with a median of only 3. The data could not be pooled on account of heterogeneity due to variable definitions and reporting formats.

An analysis exploring the effect of prior antibiotic exposure on microorganism identification was undertaken, comparing studies in which >50% versus <50% of participants had received prior antibiotics. Among seven Indian

studies with 222 children, there was no statistically significant difference between the groups in the isolation of *S. aureus* and *S. pneumoniae*. However, the prevalence of *Pseudomonas spp.* was significantly different (29.7%, 95% CI 5.9, 53.4, vs. 0.2%, 95% CI 0.0, 2.6; $P = 0.01$), confirming that it is likely associated with hospitalization, and not empyema per se.

Question 7: Which antibiotics should be administered empirically pending culture reports?

Recommendation

We recommend that in children with empyema, the antibiotics administered empirically pending culture reports should preferably be the combination of Cloxacillin and Ceftriaxone, so as to cover *S. aureus* and *S. pneumoniae*, which are the predominant bacterial species identified in Indian children with empyema (conditional recommendation, very low certainty of evidence).

Justification

This recommendation is based on three distinct lines of evidence, viz. (i) identification of *S. aureus* and *S. pneumoniae* as the predominant organisms causing empyema in Indian children (Question 6) [26], (ii) estimating the effectiveness of empiric antibiotic choices in children with empyema and (iii) the appropriateness of empiric antibiotics based on microbiologic data in various studies [27]. However, there were no studies reporting antibiotic effectiveness by assessing clinical outcomes, viz., duration of fever, persistence of fever, rise in temperature, fall in temperature, duration of ICD, and need for change in antibiotic(s).

Appropriateness of empiric antibiotics in various studies was determined by examining whether the empiric antibiotic(s) used in that study was/were effective against the organisms identified in blood and/or pleural fluid [27]. Seventeen studies with 1174 children reported this. The empiric antibiotic(s) were deemed appropriate by the EBGDG if it/they covered $\geq 80\%$ of the organisms identified, inappropriate if coverage was < 50% of the recovered organisms, unclear if 50–80% of the organisms were covered, and indeterminate if none of these options were applicable [27].

Most included studies used empirical antibiotics with activity against *Staphylococcus* and *Streptococcus* species, including cefuroxime, cloxacillin, clindamycin, ceftriaxone, amoxicillin, aminoglycosides, piperacillin-tazobactam, vancomycin, crystalline penicillin, and benzyl penicillin, either alone or in combination. The predominant pathogens isolated were *Streptococcus* and *Staphylococcus* species. Empirical antibiotic therapy was considered appropriate in 10 of 17 studies (702 patients), inappropriate in 2 studies



(50 patients), unclear in 4 studies (272 patients), and indeterminate in 1 study (150 patients).

Among the 10 studies judged to have appropriate empirical antibiotic therapy, nine used cloxacillin and three used ceftriaxone (two studies used both). Four of these studies were conducted in India [56, 65–67]. In eight of the nine studies using cloxacillin, *S. aureus* was the predominant pathogen, whereas *S. pneumoniae* predominated in the remaining study. Among the three studies using ceftriaxone, *S. aureus* was the predominant pathogen in one study, *S. pneumoniae* in one, and both *S. pneumoniae* and *H. influenzae* in the third. Based on these findings, the EBGDG concluded that, pending microbiological results, empirical treatment with a combination of cloxacillin and ceftriaxone is the preferred regimen for children with empyema in India.

Subgroup Considerations

There was no evidence to recommend in favor of, or against, any particular antibiotic(s) or combination(s) thereof, in any subgroup of children with empyema.

Implementation Considerations

Empirical antibiotic therapy should be initiated promptly after the diagnosis of empyema, without waiting for microbiological results. Whenever possible, institutions should use local microbiological epidemiology and antimicrobial susceptibility patterns to guide empirical antibiotic selection. Although ceftriaxone has *in vitro* activity against both *S. aureus* and *S. pneumoniae*, the available evidence was insufficient to recommend ceftriaxone monotherapy. However, a recent systematic review reported that ceftriaxone was as effective as, and safer than, oxacillin for the treatment of *S. aureus* infections [68]. Therefore, where cloxacillin is unavailable, clinicians may consider ceftriaxone alone, with careful clinical monitoring. These recommendations may not be applicable in regions with a high prevalence of community-acquired methicillin-resistant *S. aureus* (MRSA). The EBGDG also noted that many children had received antibiotics before referral or hospital admission, potentially reducing culture yield; nevertheless, the panel considered these recommendations applicable in such settings, while emphasizing the need for individualized clinical judgment.

Monitoring and Evaluation

Appropriateness and effectiveness of empirical antibiotics should be monitored by the clinical progress, as well as microbiological findings. Clinical signs like resolution of fever, improvement in respiratory distress, volume and character of ICD output, oxygen saturation, etc., should be continuously monitored. Deterioration in clinical status,

along with culture and sensitivity results, may signal the need for an antibiotic regimen adjustment.

Research Priorities

There is a need for well-designed multicentric studies to better understand the microbial etiology and antibiotic sensitivity patterns in pediatric empyema, particularly in cases where children have already received antibiotics before referral or hospital admission.

Question 8: What is the efficacy, safety, and long-term outcome of empyema treated with short(er) i.e. ≤ 4 weeks of antibiotic therapy, compared to long(er) i.e. > 4 weeks?

Recommendation

We offer a conditional recommendation against the intervention, viz., shorter total (i.e., intravenous plus oral) duration (i.e., ≤ 4 weeks) of antibiotic therapy, hence suggest the comparison viz. longer total (i.e., intravenous plus oral) duration (i.e., > 4 weeks), in children with empyema despite the absence of evidence comparing the two approaches, on account of greater experience with the comparison, acceptability, and feasibility (conditional recommendation, no evidence).

Justification

Deep-seated infections with limited antibiotic penetration, such as liver abscess, lung abscess, osteomyelitis, empyema thoracis, and brain abscess, are traditionally treated with prolonged courses of antibiotics, typically ranging from 4–6 weeks. This duration is considered appropriate to ensure adequate microbial clearance and to prevent relapse, particularly in infections involving poorly accessible sites like the pleural space.

While prolonged antibiotic therapy carries potential downsides, including increased cost, extended hospitalization, greater risk of adverse events, and possibly increased risk of antimicrobial resistance, it may offer a safer approach in the absence of strong evidence supporting shorter regimens.

Notably, Western guidelines that recommend antibiotic courses ≤ 3 weeks for empyema are largely based on infections caused by *Streptococcus pneumoniae*. However, in the Indian setting, *Staphylococcus aureus* is more often responsible for empyema thoracis, and may require longer treatment for effective resolution.

Given the lack of adequately powered randomized controlled trials or high-quality observational studies comparing shorter vs. longer antibiotic durations [28], and in light of the prevailing local pathogen profile, the EBGDG offered a conditional recommendation advising continuing with the



current practice of using 4–6 weeks of antibiotic therapy (rather than ≤ 4 weeks) in children with empyema.

Subgroup Considerations

There was no evidence to recommend either in favor of or against shorter or longer courses of antibiotic therapy in any subgroup of children with empyema.

Implementation Considerations

This recommendation pertains to the total duration of antibiotic therapy, viz., initial intravenous route, followed by subsequent oral therapy. Whilst administering antibiotics, careful attention must be paid to appropriate dosing based on age, weight, and renal function, as well as the route of administration (intravenous or oral), depending on the clinical condition. Monitoring for potential adverse effects, especially gastrointestinal disturbances, allergic reactions, or antibiotic-associated complications, is essential throughout the course of therapy.

In addition to selecting effective antibacterial agents, achieving adequate pleural drainage is critical for clinical improvement. This may require modalities such as chest tube insertion, imaging-guided drainage, or surgical intervention.

Monitoring and Evaluation

Regular monitoring of clinico-radiological response, inflammatory markers, adverse events, potential complications, and the overall condition should be undertaken. Antimicrobial resistance patterns in the institution and community should also be monitored.

Research Priorities

Well-designed trials are needed to compare different antibiotic durations using uniform definitions and stringent inclusion/exclusion criteria. Research is also required to explore whether antibiotic therapy durations can be based on the causative organisms and whether antibiotic duration can be tailored based on clinical response and markers of resolution.

Question 9: What is the comparison of molecular methods vs culture for identifying the microbial etiology in children with empyema?

Recommendation

We offer a conditional recommendation against the intervention (molecular methods), thereby suggesting that the comparison (culture methods) be used on account of its greater specificity, i.e., lower false positive rate, potential advantages

for antimicrobial stewardship, and lower cost (conditional recommendation, very low certainty of evidence).

Justification

The body of evidence [29] was derived from nine diagnostic accuracy studies [61, 69–76] comparing molecular methods (Polymerase chain reaction) against the reference standard, viz. culture. Among eight studies whose data were pooled, polymerase chain reaction (PCR) demonstrated high pooled sensitivity of 0.98 (0.91, 0.99), but modest specificity of 0.49 (0.19, 0.75). Whilst the high sensitivity of PCR could be advantageous for pathogen detection (especially in those who have already received antibiotics), it also raises concerns about “overdiagnosis” and unnecessary antimicrobial use, particularly in low-prevalence settings. At pre-test probabilities of 10%, 50%, and 80% (effect per 1000), the test yielded a high number of true positives (98 to 784) with few false negatives (2 to 16), confirming strong rule-out capacity. However, the increase in false positives (from 459 at 10% to 102 at 80%) reflects limited specificity. The included studies also demonstrated high negative predictive value (0.90–1.0), supporting the utility of PCR in ruling out specific microbial etiologies. However, the positive predictive value varied widely (0.11–1.0), reflecting uncertainty in the interpretation of positive results. The diagnostic odds ratio was 38.23 (5.66, 231.81), suggesting overall good discriminatory ability, albeit with variability across studies. No studies reported cost-effectiveness, but molecular methods are generally associated with higher costs compared to culture. The superior specificity of culture methods aligns better with the goals of antimicrobial stewardship and targeted treatment. The overall certainty of the evidence was rated very low due to methodological limitations, imprecision, and inconsistency.

Subgroup Considerations

There was no evidence to recommend either in favor of or against molecular methods or culture in any specific subgroup of children with empyema.

Implementation Considerations

This recommendation applies to settings where accurate microbial etiology is essential for guiding appropriate antimicrobial therapy. While molecular methods (e.g., PCR) offer the advantages of high sensitivity, rapid turnaround time, potential to detect pathogens despite prior antibiotics, and possibly detection of fastidious organisms, their lower specificity may lead to inappropriate antimicrobial choices.



Those opting to use molecular methods should be aware that despite their feasibility in many laboratories, the methods require specialized equipment, trained personnel, and stringent quality control to ensure reliability. Clinicians should interpret positive PCR results in conjunction with clinical findings and, where possible, confirmatory culture.

The choice between molecular and culture methods in specific situations/settings may be guided by test availability, laboratory infrastructure, turnaround time, cost, and potential consequences of diagnostic errors. In certain situations, molecular methods and culture may have complementary roles, without one necessarily replacing the other.

Monitoring and Evaluation

Health facilities should track whether test results of culture or PCR lead to appropriate treatment decisions on starting/cessation of therapy, turnaround time, false positives (especially with PCR), and also ensure that laboratories follow proper quality standards.

Research Priorities

Priority areas for future research include well-designed prospective diagnostic accuracy studies and economic evaluations, comparing PCR (limited to specific organisms) with culture methods.

Question 10: Should thoracic CT scan or ultrasonography be used routinely for the management of children with empyema?

Recommendation

We offer a conditional recommendation against the intervention (CT scan), thereby recommend that the comparison (ultrasonography) should be used routinely for the management of children with empyema, as the very limited data did not suggest that ultrasonography was inferior to CT scan, the absence of radiation in USG is an advantage, USG is associated with lower costs which may enhance equity, there is no need for contrast (and its associated risks), there may be no need for sedation (and its associated risks), there may be no need for patient transport, and it can be performed as and when required including multiple times in each child (conditional recommendation, very low certainty).

Justification

Only one observational study [77] with 13 children was included in the systematic review [30]. The certainty of

evidence was judged very low. The limited data suggested no substantial benefit of using CT over USG. This, combined with the knowledge of risks with radiation exposure, indirect evidence that CT may miss some pleural fluid findings which are identified on USG, larger costs associated with CT scanning, the need to transfer children, and the requirement of sedation in young children, led the EBGDG to recommend against the routine use of CT scan. In comparison, ultrasonography (USG) is a safer modality, can be performed at the bedside, can be repeated as needed without radiation risk, and is useful for guiding procedures such as ICD placement. The recommendation is conditional as the overall certainty of evidence is very low.

Subgroup Considerations

There was no evidence to recommend either in favor of or against the routine use of CT scan or USG in any specific subgroup of children with empyema.

Implementation Considerations

Although ultrasonography has many advantages, it is highly operator-dependent and requires trained personnel for accurate interpretation. However, CT scans are less practical for frequent or emergency use. CT is typically considered when ultrasound and chest X-ray findings are inconclusive or when there is no (or partial) clinical response; it also emphasizes that the impact of vaccination against *S. pneumoniae* may be lower than in other healthcare systems, particularly if pleural fluid cannot be aspirated, tube thoracostomy is not beneficial, or detailed anatomical information is required to guide further management or surgical intervention. These decisions should be made on a case-by-case basis.

Monitoring and Evaluation

Regular clinical monitoring is essential in empyema management irrespective of which imaging modality is used.

Research Priorities

Well-designed comparative studies are needed to determine whether the use of CT offers any advantage in terms of patient-centric outcomes. However, ethical considerations, particularly the risk of radiation exposure, must be carefully considered.

Question 11: What are the predictors (clinical features, radiological features, biomarkers, microbiological features, pleural pus characteristics, or combinations thereof) associated with failure of medical management or need for surgical management in children with empyema?



Recommendation

We are unable to recommend any clinical feature(s), or radiological feature(s), or biomarkers, or microbiological feature(s), or pleural pus characteristic(s), or combinations thereof, as predictors associated with failure of medical management, or need for surgical management, in children with empyema, as there was insufficient evidence; although the following three features showed statistically significant association: (a)“Sick enough to require ICU admission” (timepoint is unclear), (b)“Absence of complex septations at baseline USG”, (c)“Positive blood culture” (timepoint is unclear) (conditional recommendation, very low certainty).

Justification

The evidence synthesis [31] compared the proportions of each “predictor” among those with treatment failure versus those without treatment failure. Treatment failure was defined *a priori* as the need for escalation of care—such as chest tube insertion, surgical intervention, or ICU transfer—due to persistent or worsening symptoms despite initial antibiotic therapy.

A single study [78] identified three statistically significant potential predictors of treatment failure. These were (i) “sick enough to require ICU admission” (however, the time point was not mentioned, and the criteria were not given); (ii) “absence of complex septations” at baseline USG; and (iii) “positive blood culture” (at an unknown time point). The overall certainty was very low, as exposures were assessed only once rather than longitudinally, and outcome assessors were not blinded to exposure status. Overall, the small sample size, retrospective design, and lack of validation in independent cohorts limited their generalizability and clinical utility.

There were no studies reporting an association of treatment failure with any blood or pleural fluid biomarkers.

Subgroup Considerations

There was no evidence to recommend any predictor(s) or combination thereof in any subgroup of children with empyema.

Implementation Considerations

Given the insufficient evidence to support any predictors of medical management failure in pediatric empyema, it is prudent to closely monitor clinical symptoms (fever, respiratory distress, other respiratory signs, general well-being, appetite) as well as other indicators of overall sickness status to guide timely escalation of care if necessary.

Monitoring and Evaluation

General monitoring should assess clinical symptoms in all patients. In addition, audits of pediatric empyema can track clinical outcomes, treatment timelines, and decision-making factors.

Research Priorities

Prospective, multicenter studies using standardized definitions of treatment failure and consistent timing for clinical, radiological, and microbiological data collection are required.

Discussion

The development of this evidence-based guideline followed contemporary methodology with an emphasis on efficiency, economy, and excellence. It is significantly different from the limited guidance provided in previous documents [10–18] in its emphasis on methodological rigor, critical appraisal of evidence, consideration of diverse stakeholder perspectives, and focus on the healthcare setting in India (and similar resource-constrained health systems).

One of the notable features is the inclusion of eleven systematic reviews, including two evidence syntheses addressing the microbial etiology of empyema in India and identifying empirical antimicrobial therapy suitable for our country [26, 27]. The systematic review on etiology identified *S. aureus* as the dominant etiological pathogen in India, in stark contrast to *S. pneumoniae* in other countries [26]. This has significant ramifications for the choice of antibiotic therapy [27], duration of treatment, pleural pus drainage approaches, and the clinical outcomes.

Similarly, unlike developed countries where there is equipoise between medical and surgical approaches, the evidence-to-decision framework is clearly inclined towards medical management in India [23], although more research is required to confirm the best strategy for administering IPFT [24–28].

Two other recommendations in this guideline merit attention, viz., the emphasis on using traditional culture methods (over molecular methods) [29] and ultrasonography (over CT scanning) [30]. This is expected to significantly reduce unnecessary costs associated with empyema management.

It is anticipated that this evidence-based guideline will significantly alter the management paradigms of childhood empyema across all levels of healthcare, in both the public and private sectors of our country. A (pre-guideline) baseline nationwide survey of empyema



management practices [9] showed wide variations in clinical practice amongst Indian pediatricians, which emphasizes the importance of this evidence-based guideline and its recommendations. The survey will be repeated twice after the guideline is disseminated to evaluate short-term and long-term changes in practice and identify implementation challenges.

Meanwhile, the EBGDG will work on four other (lower) priority questions identified during the topic prioritization process and scan the literature for any new evidence necessitating updating of the current recommendations.

Conclusion

This pediatric empyema management guideline, developed using robust scientific methodology, offers evidence-based practice and policy recommendations for the management of empyema thoracis in children across all healthcare institutions in developing countries.

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Author Contributions JLM conceptualized the guideline, prepared the methods, trained the Evidence-Based Guideline Development Group (EBGDG), supervised all steps of the guideline process (viz. framing questions, prioritizing questions, evidence synthesis (in teams), appraisal of evidence, translating evidence-to-decisions, and framing recommendation statements), drafted and revised the manuscript, finalized the manuscript, and will act as guarantor. DA, SaB, KB, SoB, PC, NSC, RRD, HM, SG, PK, RK, HK, JK, SaK, SPK, AK, KK, SoK, PM, PP, MSP, SSR, MR, VS, NS, SaS, SoS, ShS, and AT served as members of the Evidence-Based Guideline Development Group and participated in framing questions, prioritizing questions, evidence synthesis (in teams), appraisal of evidence, translating evidence into decisions, and framing recommendation statements. LJ, DK, MM, AP and MS participated in evidence syntheses through systematic reviews

(all steps), critical appraisal of the evidence using GRADE methodology, and preparing evidence profiles for the evidence-to-decision framework. ND, PM, AA, and AB contributed their subject expertise to framing the questions, sharing clinical experience in empyema, reviewing the draft recommendations, and editing the guideline. All authors gave critical input and approved the final version of the guideline submitted for publication. VK and YP were the President and Secretary General (respectively) of the Indian Academy of Pediatrics (2025).

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Data Availability Data will be available upon reasonable request.

Conflict of Interest None.

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