Use of fibrinolytics and deoxyribonuclease in adult patients with pleural empyema: a consensus statement

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Although our understanding of the pathogenesis of empyema has grown tremendously over the past few decades, questions still remain on how to optimally manage this condition. It has been almost a decade since the publication of the MIST2 trial, but there is still an extensive debate on the appropriate use of intrapleural fibrinolytic and deoxyribonuclease therapy in patients with empyema. Given the scarcity of overall guidance on this subject, we convened an international group of 22 experts from 20 institutions across five countries with experience and expertise in managing adult patients with empyema. We did a literature and internet search for reports addressing 11 clinically relevant questions pertaining to the use of intrapleural fibrinolytic and deoxyribonuclease therapy in adult patients with bacterial empyema. This Position Paper, consisting of seven graded and four ungraded recommendations, was formulated by a systematic and rigorous process involving the evaluation of published evidence, augmented with provider experience when necessary. Panel members participated in the development of the final recommendations using the modified Delphi technique. Our Position Paper aims to address the existing gap in knowledge and to provide consensus-based recommendations to offer guidance in clinical decision making when considering the use of intrapleural therapy in adult patients with bacterial empyema.

Introduction

Each year, approximately 1 million patients in the USA are hospitalised with pneumonia.[1,2] Of these individuals, 20–40% develop parapneumonic effusions, of whom 5–10% develop empyema.[1] There are approximately 80 000 annual cases of pleural infections in the USA and UK combined.[3,4] Despite optimal management, the 1-year mortality from empyema is 10–15%.[5,6]

Parapneumonic effusions evolve through a spectrum of three stages.[2] The initial exudative stage (stage 1; analogous to simple parapneumonic effusion) is characterised by an increased outpouring of fluid into the pleural space mediated by capillary permeability. If left untreated, persistent inflammation with the associated rise in fluid plasminogen activator inhibitor causes a decrease in fluid fibrinolytic concentrations.[7] During this second stage (stage 2; fibrinopurulent stage), as the effusion becomes infected, septations and adhesions induced by fibrin deposition divide the space into pockets or locules. With the proliferation of fibroblasts and the formation of a pleural peel, lung expansion becomes restricted and can result in a non-expandable lung. It is important to initiate all medical treatment before this final so-called organising stage (stage 3) ensues. With the formation of a fibrous peel, the likelihood of improvement without surgery is low. The management of both complicated parapneumonic effusions (ie, not overtly purulent fluid, with pH <7·2, glucose <40–60 mg/dL, and lactate dehydrogenase >1000 IU/L) and thoracic empyema (ie, pus in the pleural space or a positive Gram stain or culture of pleural fluid) is largely the same. For simplicity, we refer to both conditions as empyema throughout this Position Paper.[3]

The treatment of empyema requires prolonged antibiotics and drainage of the pleural cavity. Although pleural septations, loculations, or high fluid viscosity can pose challenges to adequate drainage in many patients, only around 15% of patients eventually need surgery, as evidenced from the placebo groups in the MIST1 and MIST2 trials.[5,6] The landmark MIST2 trial was a multicentre, blinded, two-by-two factorial trial, in which 210 patients were randomly assigned to receive a combination of tissue plasminogen activator (tPA) and deoxyribonuclease (DNase), tPA alone, DNase alone, or placebo. Combined use of tPA and DNase improved fluid drainage (as assessed radiographically), and decreased surgical referral rates and length of hospital stay.[6]

Although understanding of the pathogenesis and microbiology of pleural infections has improved considerably in the past two decades, several questions remain regarding the optimal management of this condition. The British Thoracic Society last released a recommendation on the management of pleural infections in 2010, before the publication of the MIST2 trial.[3] In 2015, a consensus statement by the European Association for Cardio-Thoracic Surgery suggested that intrapleural fibrinolysis should be reserved for patients who are unsuitable for surgical intervention and single lung ventilation.[8] In 2017, the American Association for Thoracic Surgery recommended against routine use of fibrinolytics in patients with empyema, yet did not go into details on appropriate use.[1] It has been almost a decade since the publication of the MIST2 trial;[6] however, there is still no consensus on routine use, dosing regimens, timing of use, and the overall role (partly driven by cost) of intrapleural fibrinolytics. A few publications have assessed different regimens, but overall guidance is missing. This Position Paper addresses this gap in knowledge by focusing on important issues relating to the use of intrapleural therapy

Key messages

This consensus statement addresses various aspects of intrapleural fibrinolytic and DNase therapy in the management of adult patients with pleural empyema.

Use of intrapleural fibrinolytic or DNase monotherapy to reduce surgical referral rates
- We suggest that monotherapy with fibrinolytics should not be used as a first-line approach
- We recommend against the use of monotherapy with DNase

Use of combination therapy with a fibrinolytic agent and DNase over either fibrinolytic monotherapy or antibiotics and tube thoracostomy to reduce surgical referral rates
- When intrapleural therapy is considered, we recommend the use of combination therapy with a fibrinolytic agent and DNase

Dosing regimen of intrapleural fibrinolytics and DNase
- We suggest that 5 mg DNase should be used twice daily
- We suggest that 10 mg tPA should be used twice daily

Sequence of administering intrapleural fibrinolytics and DNase to reduce surgical referral rates
- We suggest that intrapleural fibrinolytics and DNase should be administered concurrently

Duration of chest tube clamping after administration of intrapleural fibrinolytic and DNase
- We suggest that the chest tube should be clamped for at least 1 h after administration of intrapleural fibrinolytic and DNase therapy

Dosing regimen of intrapleural fibrinolytic and DNase
- We suggest that the number of doses should be individualised on the basis of clinical (eg, trends in serum inflammatory markers, fever curve, and white cell count) and radiographic (eg, effusion improvement on chest radiography and bedside ultrasonography) response to treatment

Use of intrapleural fibrinolytics in patients with coagulopathy or on antiplatelet agents or anticoagulants
- In patients on antiplatelet agents (other than aspirin) or therapeutic anticoagulation, we suggest that the medication is held before administration of intrapleural fibrinolytics if it is clinically feasible and appropriate
- In patients with clinically significant systemic coagulopathy, we suggest avoiding fibrinolytics unless the coagulopathy is corrected

Use of intrapleural fibrinolytic and DNase as initial or subsequent therapy
- In patients with empyema, we suggest that intrapleural tPA and DNase can be used as either initial or subsequent therapy; this decision should be based on local expertise and the availability of minimally invasive surgical services

Initial approach (surgery or combination therapy with intrapleural fibrinolytic and DNase) when subsequent therapy is being considered
- In patients with suspected stage 2 (ie, fibrinopurulent) empyema, we suggest a trial of combination therapy with a fibrinolytic agent and DNase before considering surgery
- In patients suspected to have stage 3 (ie, organised pleural rind) empyema on the basis of chest CT scan and ultrasonographic assessment, we suggest considering a VATS-first approach when minimally invasive surgical expertise is available and surgical candidacy is confirmed

Cost considerations when choosing the primary approach
- In the absence of evidence, we suggest that cost considerations should not guide the use of intrapleural therapy with fibrinolytics and DNase over a primary surgical approach

Role of pleural irrigation with normal saline when used in addition to antibiotics and tube thoracostomy
- We suggest that pleural irrigation therapy with normal saline is considered only in patients who have contraindications to intrapleural fibrinolytic therapy and are not surgical candidates, as assessed by a thoracic surgeon

DNase=deoxyribonuclease. tPA=tissue plasminogen activator. VATS=video-assisted thoracic surgery.

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with fibrinolytics and DNase in patients with empyema. Our recommendations for the management of bacterial empyema in adults should not be extrapolated to non-bacterial effusions and empyema in children, given that these are different clinical entities.

Methods

We used expert opinion to formulate 11 questions relevant to clinicians who manage patients with empyema. When feasible, questions were formulated with the patient, intervention comparison, and outcome format. We did a literature and internet search to identify data from primary sources and from the reference lists of all identified articles. Relevant studies including adult patients were evaluated on the basis of the predefined questions. A total of 83 articles were included in our final assessment and recommendations (figure). We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to summarise relevant evidence and to develop recommendations for clinical practice.[9,10] This approach incorporates two components: the strength of the recommendation and a representation of the certainty of the evidence. Summary of evidence tables for graded recommendations are provided in the appendix (pp 1–8).

See Online for appendix

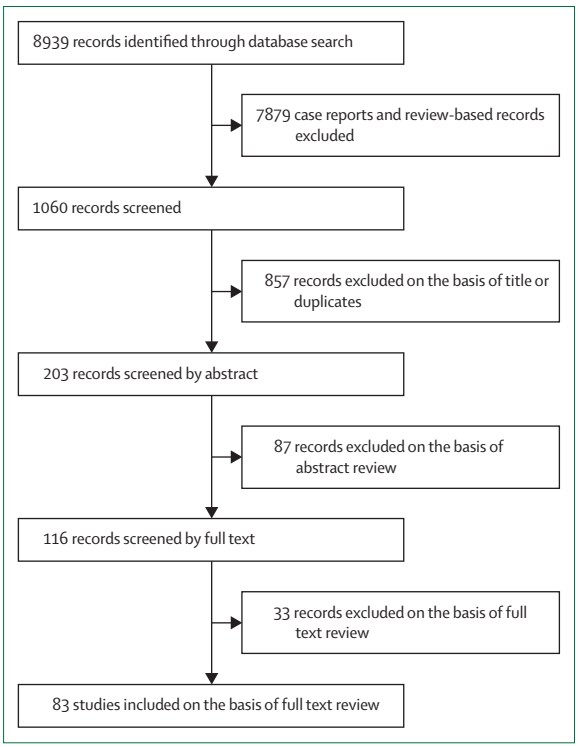

Figure: **Prisma diagram**

Consensus methodology

A core writing group (UC, AA, DF-K, VK, and NMR) first drafted distinct statements as part of the Position Paper, making recommendations. These recommendations were then circulated among all panel members, inviting opinion and any additional recommendations. The panel included 18 pulmonologists and four thoracic surgeons from 20 different institutions across five countries, all of whom had experience in managing empyema. The document was revised on the basis of comments from all 22 members. The revised document was then shared with all members and subsequently discussed during a conference call, with 64% participation (14 members). During the conference call, individual suggestions were reviewed and incorporated in real time. The modified Delphi technique, a widely accepted method for the development of consensus among experts, was used.[11–13] To achieve consensus, the decision was made a priori to conduct up to three rounds of anonymous voting or until consensus was achieved for each question, whichever came first. The survey, incorporating the questions and revised recommendations, was sent to all panel members. The panel independently and anonymously rated the appropriateness of the recommendations on a 5-point Likert scale. Consensus was defined a priori as at least 70% agreement (4 or 5 on the Likert scale), with a minimal response rate of 80%. The results of the survey were tallied and reported to the group. There was 96% survey participation (21 members) and consensus was achieved on all questions (table 1). Throughout this Position Paper, working group recommendations based on strong evidence are denoted by "we recommend". Those recommendations based on weak evidence or expert opinion are denoted by "we suggest".

Results

Question 1

In adult patients with empyema, should intrapleural fibrinolytic or DNase monotherapy be used to reduce surgical referral rates?

Recommendations

We suggest that monotherapy with fibrinolytics should not be used as a first-line approach (GRADE 2B). We recommend against the use of monotherapy with DNase (GRADE 1C).

Literature review

The use of intrapleural fibrinolytics for empyema was first described in 1949.[14] It was not until the late 1980s that there was a resurgence in the use of streptokinase for empyema.[15] Since then, several small randomised trials showing conflicting outcomes have been published.[5,6,16–25] A 2019 Cochrane review of randomised trials addressing this topic found that fibrinolytic therapy did not reduce mortality, compared with placebo (odds ratio [OR] 1·24 [95% CI 0·74–2·07]).[26] Surgical referral rates and overall treatment failure (ie, a composite of surgical referral, further fibrinolytic therapy, and mortality) were lower with fibrinolytic therapy (0·37 [0·21–0·68]) than with placebo (0·16 [0·05–0·58]). However, there was considerable heterogeneity between studies.[26] When only studies with low or unclear risk of bias were analysed, neither outcome was significantly reduced with fibrinolytic therapy.[5,6,17,19,24] This finding is consistent with the results of the largest study to address this question—the MIST1 trial.[5] In this double-blinded trial of 454 patients, streptokinase did not lead to a significant reduction in the primary outcome, a composite of death and surgical drainage at 3 months, compared with placebo (31% in the streptokinase group *vs* 27% in the placebo group; p=0·43). There was also no difference in radiographic outcomes or length of hospital stay. Although the number of adverse events was higher in the streptokinase group than in the placebo group (7% *vs* 3%; p=0·08), an equal number of patients in both groups had haemorrhage from the intervention (3% in each group). In the MIST2 study, tPA monotherapy did not improve radiographic outcomes, length of hospital stay, or surgical referral rates, compared with placebo.[6] In a small randomised trial of 20 patients, the group receiving streptokinase had more treatment failures and longer duration of hospitalisation than did the group who received surgery upfront.[27]

There are few head-to-head comparisons of fibrinolytic agents. A subgroup analysis from a 2014

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
Question 1					
We suggest that monotherapy with fibrinolytics should not be used as a first-line approach (GRADE 2B). We recommend against the use of monotherapy with DNase (GRADE 1C).	..	..	..	4 (19·05%)	17 (80·95%)
Question 2					
When intrapleural therapy is considered, we recommend the use of combination therapy with a fibrinolytic agent and DNase (GRADE 1B).	..	..	1 (4·76%)	3 (14·29%)	17 (80·95%)
Question 3					
We suggest that 5 mg DNase should be used twice daily (GRADE 2B). We suggest that 10 mg tPA should be used twice daily (GRADE 2B).	..	1 (4·76%)	..	12 (57·14%)	8 (38·10%)
Question 4					
We suggest that intrapleural fibrinolytics and DNase should be administered concurrently (GRADE 2C).	..	..	2 (9·52%)	5 (23·81%)	14 (66·67%)
Question 5					
We suggest that the chest tube should be clamped for at least 1 h after administration of intrapleural fibrinolytic and DNase therapy (GRADE 2C).	..	..	1 (4·76%)	8 (38·10%)	12 (57·14%)
Question 6					
We suggest that the number of doses should be individualised based on the clinical (eg, trends in serum inflammatory markers, fever curve, and white cell count) and radiographic (eg, effusion improvement on chest radiography and bedside ultrasonography) response to treatment (ungraded recommendation).	..	..	2 (9·52%)	7 (33·33%)	12 (57·14%)
Question 7					
In patients on antiplatelet agents (other than aspirin) or therapeutic anticoagulation, we suggest that the medication is held before administration of intrapleural fibrinolytics if it is clinically feasible and appropriate (ungraded recommendation). In patients with clinically significant systemic coagulopathy, we suggest avoiding fibrinolytics unless the coagulopathy is corrected (ungraded recommendation).	..	..	3 (14·29%)	11 (52·38%)	7 (33·33%)
Question 8					
In patients with empyema, we suggest that intrapleural tPA and DNase can be used as either initial or subsequent therapy. This decision should be based on local expertise and the availability of minimally invasive surgical services (GRADE 2C).	..	1 (4·76%)	..	14 (66·67%)	6 (28·57%)
Question 9					
In patients with suspected stage 2 (ie, fibrinopurulent) empyema, we suggest a trial of combination therapy with a fibrinolytic agent and DNase before considering surgery (ungraded recommendation). In patients suspected to have stage 3 (ie, organised pleural rind) empyema on the basis of chest CT scan and ultrasonographic assessment, we suggest considering a VATS-first approach when minimally invasive surgical expertise is available and surgical candidacy is confirmed (ungraded recommendation).	..	..	..	14 (66·67%)	7 (33·33%)
Question 10					
In the absence of evidence, we suggest that cost considerations should not guide the use of intrapleural therapy with fibrinolytics and DNase over a primary surgical approach (ungraded recommendation).	..	1 (4·76%)	1 (4·76%)	10 (47·62%)	9 (42·86%)
Question 11					
We suggest that pleural irrigation therapy with normal saline is considered only in patients who have contraindications to intrapleural fibrinolytic therapy and are not surgical candidates, as assessed by a thoracic surgeon (GRADE 2C).	..	..	1 (4·76%)	13 (61·90%)	7 (33·33%)

DNase=deoxyribonuclease. tPA=tissue plasminogen activator. VATS=video-assisted thoracic surgery.

Table 1: **Survey data assessing agreement with recommendations**

meta-analysis showed that only urokinase had a positive effect in reducing the need for surgical intervention.[28] Two randomised studies have compared fibrinolytic agents; streptokinase versus urokinase in one,[16] and alteplase versus urokinase in another.[25] In these studies, there was no difference in the mortality rate, surgical referral rate, or the composite of both of these, or in the need for further fibrinolytic therapy. In the study comparing alteplase with urokinase, there was a significantly higher number of serious bleeding events in patients who received alteplase (five [28%] of 18 patients receiving 20 mg alteplase and four [12%] of 33 patients receiving 10 mg alteplase *vs* none [0%] of 48 patients in the urokinase group).[25] In another prospective study comparing tPA and DNase with urokinase, there was no difference in the need for an additional chest tube or surgery between the groups.[29] tPA and DNase led to more haemothoraces (defined as blood in the drain) than did urokinase (seven [17%] of 41 patients *vs* none [0%] of 52 patients; p=0·002). No patient receiving tPA and DNase had a haemoglobin decrease or haemodynamic change from the haemothorax; however, it did lead to fibrinolytic discontinuation in five (12%) of these patients. A phase 1 trial of a novel fibrinolytic agent, single-chain urokinase (LTI-01), has shown safety and tolerability of this

agent.[30] Whether or not future studies of novel fibrinolytics will show greater efficacy than contemporary agents remains to be seen.

Although not a fibrinolytic, data on DNase monotherapy are scarce. The initial report by Tillet and colleagues[14] in 1949 involved the use of streptococcal DNase in addition to streptokinase. Light and colleagues[31] showed that DNase needed to be added to fibrinolytic therapy to liquefy empyema from rabbits. Similarly, studies in rabbits[32] and a randomised controlled trial[6] have shown the synergistic effect of combination therapy. Other than the two-by-two factorial MIST2 trial, there are no studies assessing the use of DNase monotherapy.[6] In MIST2, radiological improvement and length of hospital stay were similar among the DNase monotherapy group and the placebo group. However, surgical referral rates were higher with use of DNase alone than with the placebo (p=0·01). The authors hypothesised that patient deterioration in the DNase monotherapy group might have been due to systemic absorption of bacterial or inflammatory components following biofilm disruption mediated by DNase in the pleural space, with ineffective drainage due to undisrupted fibrinous septations.[6]

Rationale for recommendations

Pooled analysis from heterogeneous studies suggests reduced surgical referral rates with fibrinolytic therapy compared with placebo.[26] However, there is discordance between the results of the largest randomised trial[5] and those of this analysis.[26,28] Given the well known synergistic effect of combination therapy in animal and human studies, when intrapleural therapy is considered in patients with empyema, fibrinolytic monotherapy should not be used as first-line therapy. In institutions or circumstances where DNase is contraindicated or not available, monotherapy with a fibrinolytic agent or irrigation with saline can be considered in patients who are not surgical candidates.[33] From a single study subgroup analysis, DNase monotherapy does not seem to provide any fluid drainage benefit, and should be avoided until evidence of the contrary is shown.[6]

Question 2

In adult patients with empyema, should intrapleural combination therapy with a fibrinolytic agent and DNase be used over either fibrinolytic monotherapy or antibiotics and tube thoracostomy to reduce surgical referral rates?

Recommendations

When intrapleural therapy is considered, we recommend use of combination therapy with a fibrinolytic agent and DNase (GRADE 1B).

Remarks

tPA is the only fibrinolytic agent that has been studied in combination with DNase. There are insufficient data to make definitive conclusions on the use of tPA and DNase in patients with an indwelling pleural catheter and pleural space infection that is inadequately drained, despite continuous drainage. However, until evidence of the contrary is available, we suggest that tPA and DNase can be used in these patients.

Literature review

Where fibrinolytics break septations and create a possible lavage effect through pleural fluid production,[34,35] DNase works synergistically by reducing fluid viscosity by breaking down the extracellular uncoiled DNA from dead leucocytes and bacteria. Another possible mechanism of synergy could be improved antibiotic penetration through breakdown of biofilms incorporated with fibrin and DNA.[36] The concept of how these agents work in synergy and enable improved drainage of empyema collections has been proven in animal and human studies.[6,32] The MIST2 trial showed that combination therapy with tPA and DNase resulted in enhanced fluid drainage (and consequent radiological improvement), a reduced need for surgical interventions (4% with combination therapy *vs* 16% with placebo; p=0·03; representing a 77% lower surgical referral rate), and a shorter hospital stay (median –6·7 days compared with placebo; p=0·006), without an increase in adverse events.[6] A limitation of the MIST2 trial, as acknowledged by the authors of the study, is that the primary outcome of radiographic improvement from baseline cannot be assumed to be a true treatment effect.

The benefits of combination intrapleural therapy with tPA and DNase have been subsequently shown in other non-randomised settings. A multinational, observational study of 107 patients showed the safety and efficacy of this approach.[37] In this study, 99 (92%) of 107 patients who did not respond to standard therapy with antibiotics and chest tube drainage could be managed with combination therapy without the need for surgical intervention. Subsequent studies, including 50–100 patients, have all shown that approximately 90% of patients treated with combination therapy can be managed without surgery.[38–41] In these studies, radiological improvement and safety were also shown.

Patients with malignant pleural effusions managed with an indwelling pleural catheter can develop infections in the pleural space. These patients, with limited survival, are often not surgical candidates. Evidence to support the use of tPA and DNase in patients with an indwelling pleural catheter comes from only six individuals in a retrospective review of 50 patients.[42]

Rationale for recommendations

tPA and DNase combination therapy is safe, reduces surgical referrals, improves fluid drainage (as assessed by chest radiography), and reduces length of hospital stay. Along with the widespread availability of these medications and their ease of administration through even a small-bore chest tube, these results make combination therapy with a fibrinolytic agent and DNase

an essential first-line approach in patients with empyema, in whom intrapleural therapy is being considered.

Differences in biology between a primarily infected pleural space and empyema secondary to an indwelling pleural catheter might account for differences in efficacy and safety of tPA and DNase in these two populations. Until evidence of the contrary is available, it might be reasonable to consider tPA and DNase use in patients with empyema secondary to an indwelling pleural catheter when continuous drainage and appropriate antibiotics are not effective, with close monitoring of pleural fluid output.

Question 3

In adult patients with empyema, what dosing regimen of intrapleural fibrinolytics and DNase should be used?

Recommendations

We suggest that 5 mg DNase should be used twice daily (GRADE 2B). We suggest that 10 mg tPA should be used twice daily (GRADE 2B).

Remarks

There is weak evidence to suggest that starting with 5 mg tPA might be as effective as 10 mg tPA. If 5 mg tPA is administered, dose escalation to 10 mg should be considered if clinical and radiological improvement is not seen.

There is weak evidence to suggest that once or twice daily instillation of intrapleural tPA and DNase have similar efficacy and safety. If a once daily regimen is selected, we suggest that changing to twice daily dosing should be considered if clinical and radiological improvement is not seen.

Literature review

The MIST2 trial used 5 mg DNase on the basis of a single case report[43] and previous experience in four patients. This dose has since been used in most studies exploring DNase for management of empyema.[27,29,37–41] A small retrospective study used 10 mg DNase concurrently with 4 mg tPA and reported no major adverse events.[44] No other studies have compared different doses of DNase.

Various dosing regimens of tPA have been investigated. However, there has been no major difference reported in surgical referral rates, length of hospital stay, inflammatory marker change, or radiological outcomes. Most studies exploring tPA have used 10 mg, a dose empirically selected in the MIST trials. In most studies, including the landmark MIST2 trial[6] and the study by Piccolo and colleagues,[37] in which intrapleural therapy was administered as subsequent therapy in 90 (84%) of 107 patients, tPA and DNase were administered twice daily. Mehta and colleagues[38] used once daily dosing of tPA and DNase and were able to avoid surgical intervention in 51 (93%) of 55 patients. Alemán and colleagues[25] started with a daily dose of 20 mg tPA alone, but switched mid-protocol to 10 mg after encountering serious bleeding events in five (28%) of 18 patients. In another study, in which tPA alone was used as a 25 mg daily instillation, two patients had bleeding events; however, this and other adverse events were not significantly different compared with the placebo group.[24] Popowicz and colleagues[41] tried an initial dose of 5 mg tPA, allowing dose escalation to 10 mg, at the discretion of the treating physician. After an average of 3·3 doses, seven (12%) of 61 patients required dose escalation. There was no difference in length of hospital stay in individuals who required dose escalation. Overall, 57 (93%) of 61 patients avoided surgery and were discharged alive (at 1 month). Three patients (5%) had bleeding events requiring blood transfusions.

Studies investigating urokinase used a dose of 100 000 IU once daily,[16,18,19,25] except for one that used 250 000 IU twice daily.[29] The studies investigating streptokinase mainly used 250 000 IU daily.[16,17,20,21] In the MIST1 trial, 250 000 IU of streptokinase was administered every 12 h,[5] whereas it was dosed as 2·5 million IU daily in another study.[22] Medications are mixed in 20–100 mL of normal saline for administration. This regimen should be followed by a normal saline flush to push the drug out of the chest tube and into the pleural cavity.

Rationale for recommendations

Although there have been no large studies addressing different doses of DNase, tPA has been used in doses of 5–25 mg with once or twice daily administration. However, none of the major outcomes or complications varied significantly among the 5–10 mg doses or the once or twice daily dosing frequency. tPA is sensitive to inhibition by plasminogen activator inhibitor-1 (PAI-1), and effective dosing of tPA monotherapy would need to rely on dose escalation studies that have not yet been done. Therefore, until evidenced by stronger data, we recommend following the dosing regimens used by the MIST2 trial.[6] To date, the best dosing and schedule at which intrapleural therapy should be given has not been rigorously studied. Future recommendations could change as new agents enter dose ranging phase 2 testing.

Question 4

In adult patients with empyema, should intrapleural fibrinolytics and DNase be administered sequentially or concurrently to reduce surgical referral rates?

Recommendations

We suggest that intrapleural fibrinolytics and DNase should be administered concurrently (GRADE 2C).

Remarks

The rationale for this recommendation is that concurrent dosing is less cumbersome than sequential dosing, in the absence of evidence showing a difference in efficacy.

Literature review

Fixed-dose combination of medications decreases medication non-compliance.[45] The empirically chosen sequential administration of tPA and DNase in the MIST2 trial is cumbersome and requires the provider to access the patient's chest tube a minimum of six times in the day (eg, tPA administration plus clamp, followed by DNase administration plus clamp, followed by unclamping, followed by repeating the process). This type of administration might have partly accounted for the 71% compliance with trial medications reported in this study.[6] A single-centre, retrospective cohort study of 73 patients first showed that concurrent dosing was safe and effective.[39] Surgery was avoided in 66 patients (90%). Bleeding requiring transfusion occurred in four patients (5%) and pain requiring analgesia dose escalation occurred in 11 patients (15%). These outcomes are similar to those of studies investigating sequential dosing. This study[39] was followed by a prospective observational study of 38 patients at the same institution, of whom 20 received tPA and DNase concurrently.[46] Clinical and radiological improvement without the need for surgery was similar across both groups (78% in the concurrent group *vs* 75% in the sequential group; p=0·57). This rate of treatment success is lower than that of previous publications. The authors attribute such to the regular use of ultrasound (thereby detecting smaller fluid pockets with higher sensitivity) and a reduced institutional threshold for referring patients to video-assisted thoracic surgery (VATS). Three other small retrospective studies of 17, 23, and 39 patients have reported concurrent administration of tPA and DNase to be safe and effective.[44,47,48]

Rationale for recommendations

Although it is unknown whether or not concurrent intrapleural administration of tPA and DNase affects the pharmacokinetics of either drug, it can be assumed that concurrent and sequential dosing are equally safe and effective on the basis of weak evidence. Additionally, concurrent dosing decreases the amount of time in the day that the chest tube remains clamped, and could possibly result in improved provider compliance and reduced risk of iatrogenic infection by decreasing the frequency with which the chest tube needs to be accessed. Further studies that carefully analyse pleural fluid are needed to assess the biochemical synergy of tPA and DNase in the pleural space.

Question 5

In adult patients with empyema, how long should the chest tube be clamped after administration of intrapleural fibrinolytic and DNase?

Recommendations

We suggest that the chest tube should be clamped for at least 1 h after administration of intrapleural fibrinolytic and DNase therapy (GRADE 2C).

Remarks

So-called dwell time of more than 4 h has not been studied.

Literature review

Across studies, there is high variability in practice in terms of duration of chest tube clamping after instillation of fibrinolytics and DNase (ie, dwell time). Dwell times of 40–60 mins,[37] 1 h,[6,24] 2 h,[17,20,25] 3 h,[18] and 4 h[21,49] have been used. Irrespective of the dwell times, efficacy and safety outcomes across all studies were similar. Currently, no pooled analysis is available addressing this question and there are no head-to-head comparisons.

Rationale for recommendations

Due to heterogeneity in other interventions and the type and dose of intrapleural agents used, making recommendations for choosing a particular dwell time over another is not possible. The systemic half-life of tPA in the blood is only 3–5 mins, whereas that of DNase is 3–4 h.[15,50] The systemic elimination of urokinase and streptokinase is also rapid. However, the pharmacokinetics of these drugs in the pleural space is still undetermined, making accurate recommendations of optimal dwell times challenging. Until further evidence is available, given the short half-lives of these drugs, we recommend using a dwell time at least equivalent to that used in the MIST2 trial.[6]

Although the appropriate size of chest tube continues to be a matter of debate,[51] we suggest that a 12–16F chest tube is inserted in adult patients with empyema. When small bore tubes are used, frequent (ie, every 6–8 h) normal saline flushes should be administered to ensure patency.[3]

Question 6

In adult patients with empyema, should a fixed number of doses or an individualised regimen of intrapleural fibrinolytic and DNase be used?

Recommendations

We suggest that the number of doses should be individualised on the basis of the clinical (eg, trends in serum inflammatory markers, fever curve, and white cell count) and radiographic (eg, effusion improvement on chest radiography and bedside ultrasonography) response to treatment (ungraded recommendation).

Remarks

There is insufficient evidence to recommend a fixed number of doses.

Literature review

In the MIST2 study, patients randomly assigned to the treatment groups received six doses over 3 days.[6] However, only 32 (67%) of 48 patients in the combination group received all six doses. Combination therapy showed a

significant reduction in white cell count and log odds of fever, and a non-significant reduction in C-reactive protein (CRP), compared with placebo. The mean difference in pleural opacity from day 1 to day 7 in the tPA and DNase group (–29·5%) and the placebo group (–17·2%) was significant.

In a study by Piccolo and colleagues,[37] 25 (23%) of 107 patients did not receive all six doses. Pleural opacity on chest radiography was reduced from a median of 35% of the hemithorax to 14%. There was a 40% reduction in CRP by day 5 from its baseline concentration before treatment. In a study by Popowicz and colleagues,[41] clinical resolution resulted in early treatment discontinuation in 22 (36%) of 61 patients (median of three doses). The percentage of hemithorax occupied by pleural opacity was reduced from a median of 42% on baseline chest x-ray to 16% after at least 3 days. By day 4 of treatment, there was a 45% median reduction in CRP from its baseline concentration. In a study by Majid and colleagues,[39] the median number of doses administered was only two (IQR 1·0–3·5).

In a retrospective study evaluating the role of extending therapy beyond six doses, with 20 individuals in the extended dose group and 81 individuals in the standard dose group, there was no significant difference in surgical referral rates or bleeding rates between the groups.[40]

Rationale for recommendations

When feasible, a baseline chest CT scan, ideally with intravenous contrast, should be obtained in all patients. Daily chest x-ray, bedside ultrasonography, or both, should be used to assess the suitability and timing of intrapleural fibrinolytic and DNase therapy, and the response to it. Patients might respond to a median of 2–3 doses or might occasionally need extended dosing.[39,40] The need for every successive dose should be established by reviewing the response to the previous dose. Response is assessed clinically (eg, by reviewing the patient's fever curve, white cell count, and CRP concentration) and radiologically (eg, best assessed by a combination of chest radiography and bedside ultrasonography). Ultrasound can identify smaller fluid pockets with greater sensitivity than chest x-ray and can visualise septations better than CT.[52] The absence of a clinically significant response after 24–48 h should not justify ongoing dosing to complete a pre-decided treatment course. Similarly, patient tolerability before each successive dose must be factored in. When fluid output is low despite tPA and DNase, chest CT should be reconsidered to accurately assess response to therapy, ensure appropriate chest tube position, and evaluate for multiloculated collections. The persistence of fluid collection observed on imaging, non-responsiveness to treatment with persistent sepsis, or both, as well as the inability of the lung to fully re-expand (leaving a potential space for recurrent infection), should be triggers for surgical referral or additional image-guided chest tube placement.

Question 7

In adult patients with empyema, can intrapleural fibrinolytics be used in patients with coagulopathy or on antiplatelet agents or anticoagulants?

Recommendations

In patients on antiplatelet agents (other than aspirin) or therapeutic anticoagulation, we suggest that the medication is held before administration of intrapleural fibrinolytics if it is clinically feasible and appropriate (ungraded recommendation). In patients with significant systemic coagulopathy, we suggest avoiding fibrinolytics unless the coagulopathy is corrected (ungraded recommendation).

Remarks

In patients with a prohibitive risk of bleeding, tPA and DNase might be used with caution in patients who are not surgical candidates, after a detailed multidisciplinary risk–benefit discussion. Prophylactic doses of anticoagulation do not generally increase the risk of bleeding with fibrinolytics.

Literature review

Given the high molecular weight and short half-life (3–5 mins in plasma) of fibrinolytics such as tPA, the systemic absorption of the drug is limited by intrapleural administration.[15] A study analysing the systemic fibrinolytic effects of intrapleural streptokinase with a 2 h dwell time showed no difference in prothrombin time, activated partial thromboplastin time, thrombin time, or fibrinogen and D-dimer concentration.[53] Bleeding risk with fibrinolytics is thought to be the highest in patients who have pre-existing risk factors, such as individuals with coagulopathy due to liver or renal failure, with thrombocytopenia, or who are on systemic anticoagulation. Coincidental stroke, major haemorrhage or trauma, or major surgery in the previous 5 days were exclusion criteria for patients in the MIST2 trial.[6] No randomised trials have been done to specifically address whether or not administration of intrapleural fibrinolytics in patients on systemic anticoagulation increases bleeding risk.

Although systemic bleeding is rarely reported in the literature, intrapleural bleeding can be seen in 0–5% of patients with empyema treated with intrapleural fibrinolytics.[6,37,39,46] In the MIST2 trial, three (6%) of 52 patients had adverse events related to bleeding in the tPA–DNase group, with two cases of intrapleural bleeding and one case of haemoptysis.[6] In a retrospective study of 66 patients, all four patients who had major pleural bleeding were noted to be in the therapeutic anticoagulation group (N=12).[54] None of the 38 patients on prophylactic anticoagulation had bleeding. In a retrospective study of 30 patients with malignant pleural effusion who received intrapleural fibrinolytic therapy and were on concurrent anticoagulation, two (6%) experienced pleural bleeds requiring transfusion.[55]

However, it is important to note that the median number of doses was one, the most frequent dose was 25 mg of tPA, and that only one patient received six doses of tPA. Of the four patients (5%) who had bleeding in a study by Majid and colleagues,[39] one individual had a history of liver cirrhosis, and another had atrial fibrillation being treated with anticoagulation. Table 2 summarises the major studies reporting bleeding events with intrapleural fibrinolytic administration.

Popowicz and colleagues[41] acknowledged the bleeding risk with tPA and sought to evaluate the safety of a lower dose (ie, 5 mg). However, bleeding rates were similar to those reported for 5 mg in previous publications (4·9%). There is plausible evidence from two trials to suggest that bleeding rates with urokinase are lower than those with tPA. In a randomised trial, five (28%) of the 18 patients who received 20 mg alteplase and four (12%) of the 33 patients who received 10 mg alteplase had bleeding.[25] In another study, tPA led to haemothoraces (defined as blood in the drain) in seven (17%) of 41 patients.[29] None of the patients receiving tPA and DNase had a haemoglobin drop or haemodynamic change from the haemothorax; however, five (12%) of these patients had fibrinolytic discontinuation. In both of these studies, no patient on urokinase had a bleeding event.

Rationale for recommendations

The risk of intrapleural bleeding with fibrinolytics appears to be increased in patients on systemic therapeutic anticoagulation and in individuals with coagulopathy. Although there are no data to suggest increased bleeding risk in patients on antiplatelet agents such as clopidogrel, prasugrel, or ticagrelor, it is reasonable to exercise caution until further evidence is available. Specific cutoffs of prothrombin time, activated partial thromboplastic time, and platelet counts, which should contraindicate intrapleural administration of fibrinolytics, cannot be established from existing literature. However, despite the fact that intrapleural bleeding events might require surgery or blood transfusion, they rarely lead to haemodynamic changes or death. Although there appears to be a dose-dependent risk of bleeding, doses of less than 10 mg tPA have not been shown to be safer than doses of 10 mg.

Given the available evidence, we recommend exercising caution when considering the use of intrapleural fibrinolytics in patients who are at risk of bleeding. When possible, the systemic coagulopathy should be corrected, or the anticoagulant should be held. If this is not feasible, starting with low doses (and escalating if need be) with close monitoring of pleural fluid output can be considered in patients who are not surgical candidates, after a multidisciplinary risk–benefit discussion. However, there is no evidence of reduced bleeding events with low doses.[41]

Question 8

In adult patients with empyema, should intrapleural fibrinolytic and DNase be used as initial or subsequent therapy?

Recommendations

In patients with empyema, we suggest that intrapleural tPA and DNase can be used as either initial or subsequent therapy. This decision should be based on local expertise and the availability of minimally invasive surgical services (GRADE 2C).

Remarks

Routine initial use of tPA and DNase might be considered on a case-by-case basis, only after a multidisciplinary risk–benefit discussion of such an approach. Additionally, local cost considerations must be factored into decision making.

Literature review

Initial therapy refers to fibrinolytic and DNase instillation immediately after chest tube insertion. Subsequent therapy refers to fibrinolytic and DNase use only if required (usually after 24 h) due to lack of clinical (eg, trends in serum inflammatory markers, fever curve, and white cell count) or radiological (eg, effusion improvement on chest radiography and bedside ultrasonography) response, or worsening despite appropriate antibiotics and chest tube drainage.

In the MIST2 trial, patients were randomly assigned immediately after chest tube insertion.[6] Mehta and colleagues[38] administered once daily tPA and DNase within 24 h of chest tube placement and found a mean change in pleural opacity of –28·8% (calculated as the difference between the percentage of hemithorax occupied on day 1 and day 7). Similar results were seen in a study by Majid and colleagues.[39] In this study, 52 (71%) of 73 patients received the first dose of concurrent tPA and DNase within 24 h of chest tube insertion.

Most patients (85%) with empyema can be managed with appropriate antibiotics and pleural fluid drainage via a chest tube.[5,6] tPA and DNase use as subsequent therapy was first assessed in a multicentre study by Piccolo and colleagues.[37] Most patients (84%) received their first dose more than 24 h after chest tube insertion (median of 2 days). Treatment success in this study was similar to that of studies that used tPA and DNase as initial therapy. Similarly, in the study by Popowicz and colleagues,[41] 57 (93%) of 61 patients received the first dose of intrapleural tPA and DNase therapy more than 24 h after chest tube insertion.

Rationale for recommendations

Assuming that the patient is receiving appropriate antibiotics, there should be significant clinical or radiological improvement within 24 h of chest tube insertion.[2] Only approximately 15% of patients in the

	Study type	Agent(s) studied	Incidence of overall bleeding in patients on fibrinolytics	Incidence of intrapleural bleeding in patients on fibrinolytics	Comments	Exclusion criteria relevant to increased bleeding risk
Maskell et al (2005; MIST1 trial)[5]	Double-blind, randomised controlled trial	Streptokinase	7/206 (3%)	Not described separately	Haemorrhage included local pleural or systemic bleeding	Coincidental stroke or major haemorrhage, or major surgery within previous 5 days
Rahman et al (2011; MIST2 trial)[6]	Double-blind, randomised controlled trial	tPA plus DNase	3/52 (6%)	2/52 (4%)	Bleeding reported in two (4%) of 51 patients in the DNase-only group and no patients in the tPA-only group; two patients had intrapleural haemorrhage, both in the tPA plus DNase group	Coincidental stroke, major haemorrhage or trauma, or major surgery within previous 5 days
Alemán et al (2015)[25]	Double-blind, randomised controlled trial	Urokinase *vs* alteplase	Urokinase: 0/48 (0%); alteplase: 9/51 (18%)	Urokinase: 0/48 (0%); alteplase: 7/51 (14%)	Bleeding reported in five (28%) of 18 patients who received 20 mg alteplase and four (12%) of 33 patients who received 10 mg alteplase; two patients had haemoptysis, three patients had haemothorax requiring surgery, four patients had haemothorax that resolved with supportive care	Coagulopathy, anticoagulant treatment, active haemorrhage in any location, recent puncture of a non-compressible vessel
Bédat et al (2019)[29]	Prospective cohort study	Urokinase *vs* tPA plus DNase	Urokinase: 0/52 (0%); tPA plus DNase: 7/41 (17%)	Urokinase: 0/52 (0%); tPA plus DNase: 7/41 (17%)	No patient had decreased haemoglobin or haemodynamic changes; five patients in the tPA plus DNase group had premature termination of therapy due to haemothorax (defined as blood in the drain)	NA
Piccolo et al (2014)[37]	Observational study	tPA plus DNase	2/107 (2%)	2/107 (2%)	No control group	NA
Mehta et al (2016)[38]	Retrospective study	Once daily use of tPA plus DNase	No major bleeding events	No major bleeding events	No control group	Coincidental stroke, major haemorrhage or trauma, major surgery in the previous 5 days
Majid et al (2016)[39]	Retrospective study	Concurrent instillation of tPA and DNase	4/73 (5%)	4/73 (5%)	Two patients had coagulopathy (one with cirrhosis and one on anticoagulation); no control group	NA
Popowicz et al (2017)[41]	Observational, open-label study	5 mg tPA plus 5 mg DNase twice daily, with tPA dose escalation permitted	3/61 (5%)	2/61 (3%)	One patient with chest wall haematoma had thrombocytopenia; no control group	NA
Kheir et al (2018)[46]	Prospective observational study	tPA plus DNase	Total: 2/38 (5%); sequential group: 1/18 (6%); concurrent group: 1/20 (5%)	Total: 2/38 (5%); sequential group: 1/18 (6%); concurrent group: 1/20 (5%)	No control group	NA

Data are n/N (%). tPA=tissue plasminogen activator. DNase=deoxyribonuclease. NA=not applicable.

Table 2: **Major studies reporting risk of bleeding associated with use of fibrinolytics in patients with empyema**

placebo groups of the MIST1 and MIST2 cohorts required surgical referral. Non-improvement should warrant clinical and radiological assessment and chest tube troubleshooting. The confirmation or suspicion of a multiloculated collection should warrant initiation of intrapleural fibrinolytic and DNase therapy and early surgical consultation (which might not be broadly available), such that the decision to proceed with either medical or surgical therapy is ideally made by a multidisciplinary pleural team. The presence of septations on ultrasound or loculations on chest CT might not suffice to justify initial therapy. However, this finding cannot be generalised to all patients. There is theoretical rationale for early initiation of aggressive therapy, whether that is surgery or intrapleural fibrinolytics and DNase (as used in the MIST2 trial). However, the true benefit of initial over subsequent therapy will not be known without randomised evaluation of patients. The costs and potential risks of intrapleural therapy must be considered before either approach.

Question 9

In adult patients with empyema who are considered for subsequent therapy, should surgery or combination therapy with intrapleural fibrinolytic and DNase be used first?

Recommendations

In patients with suspected stage 2 (ie, fibrinopurulent) empyema, we suggest a trial of combination therapy with a fibrinolytic agent and DNase before considering surgery (ungraded recommendation). In patients suspected to have stage 3 (ie, organised pleural rind)

empyema on the basis of chest CT and ultrasonographic assessment, we suggest considering a VATS-first approach when minimally invasive surgical expertise is available and surgical candidacy is confirmed (ungraded recommendation).

Remarks

In institutions with available expertise in minimally invasive surgery, a VATS-first approach for stage 2 empyema might be considered on a case-by-case basis. In patients with stage 3 empyema, a trial of tPA and DNase can be considered while awaiting surgical consultation.

Literature review

Despite studies showing that over 80% of patients can be managed without surgery,[5,6] some consultants continue to recommend a surgery-first approach.[1] Two randomised trials have compared tube thoracostomy with immediate VATS for patients with empyema.[27,56] One trial was a small, unblinded study of 20 patients that compared VATS with chest tube drainage plus streptokinase.[27] In this study, there were fewer treatment failures, and shorter duration of chest tubes and hospitalisation in the surgical group than in the chest tube drainage plus streptokinase group. The other trial included 70 patients and compared VATS debridement with tube thoracostomy (without the use of intrapleural fibrinolytic or DNase therapy).[56] This study noted a shorter length of stay (8·3 days *vs* 12·8 days) and less need for open surgery (17% *vs* 37%; p<0·05) in the VATS group than in the tube thoracostomy group. The need for surgical intervention in the tube thoracostomy group was higher (37%) than that reported in the placebo groups of MIST1 and MIST2 trials (14–16%).[5,6] The study was unblinded, did not have prespecified criteria for surgical intervention in the tube thoracostomy group, and did not describe use of intrapleural fibrinolytic or DNase therapy. A retrospective study assessing 78 patients, with 54 patients in the VATS group and 24 patients in the streptokinase group, noted no difference in the need for open surgery.[57] However, patients in the VATS group had a shorter length of stay than those in the streptokinase group. Another study, in which 28 patients with stage 1 empyema were managed with tube thoracostomy and 38 patients with stage 1 and 2 empyema were managed with VATS, noted reduced morbidity and length of stay in the VATS group.[58] However, the patients were not randomly assigned, and a fibrinolytic agent was used in only two (7%) of 28 patients in the tube thoracostomy group. A few centres with expertise use medical thoracoscopy as an alternative to VATS in patients with stage 2 empyema. However, there are no studies that have compared medical thoracoscopy with VATS in this population. A single-centre study of 32 patients comparing medical thoracoscopy with intrapleural tPA and DNase has established the safety of this procedure.[59]

Rationale for recommendations

The objective of surgery in empyema is to evacuate infected material and to re-expand the lung. The American Association for Thoracic Surgery recommends that VATS should be the first-line approach in all patients with stage 2 acute empyema,[1] especially in patients under the care of a dedicated thoracic surgeon. However, surgery has been associated with up to a 30% complication rate and approximately 4% mortality rate.[60–63] Besides, some series assessing VATS have tended to operate on healthier patients, as evidenced by the younger age and fewer comorbidities of these patients compared with those with empyema.[64,65] The conversion rate from VATS to open decortication is 0·0–3·5% in early-stage empyema and 7·1–46·0% in late-stage empyema.[63] Delays in referral are associated with higher conversion rates to open thoracotomy (<60%).[60–62] The largest series reported a conversion rate to open decortication of 11·4%.[66] It should also be considered that VATS can be done with only one or two ports, making the incremental invasiveness of a VATS approach compared with medical therapy much smaller than that of thoracotomy compared with medical therapy. A detailed review of VATS versus open thoracotomy is beyond the scope of this Position Paper. Although there is one small study comparing medical thoracoscopy with tPA and DNase,[59] routine use of this procedure in patients with empyema requires large, multicentre, randomised controlled, prospective validation.

There is only one randomised trial addressing the question of surgery versus intrapleural fibrinolytic therapy first in patients with empyema.[27] Although studies show a shorter hospital stay with surgery than with fibrinolytics, an improvement in any other clinical outcome cannot be inferred from the available data. No studies in adults have compared VATS with a combination therapy of a fibrinolytic agent and DNase. Although the identification of a pleural rind (ie, stage 3 empyema) is an uncontroversial indication for surgery, routine decortication in patients with pure stage 2 empyema appears to be unnecessary. Patients who receive combination intrapleural therapy with a fibrinolytic and DNase need surgical interventions in up to 10% of cases.[5,6,37–41] Therefore, a routine surgery-first approach will lead to procedures in many more patients than would need it. Even the placebo group in the MIST1 and MIST2 trials needed surgical referral in only 15% of cases.[5,6] However, in clinical practice, establishing a firm dichotomy between stage 2 and 3 is challenging.[1] In patients who are not improving or worsening (ie, medical treatment failure), with uncontrolled sepsis, any risk of surgery is outweighed by the potential benefit that might be attained.

Despite years of experience with either approach, this question remains an extensively debated area and we still do not know what the optimal initial treatment for

empyema is. Ongoing trials (eg, NCT03584113, NCT03583931, NCT02165891, and ISRCTN18192121) will try to better answer this question. Long-term outcomes and patient quality of life after either intervention has not been adequately studied.

Question 10

In adult patients with empyema, should the use of intrapleural therapy with fibrinolytics and DNase be preferred over a primary surgical approach on the basis of cost considerations?

Recommendations

In the absence of evidence, we suggest that cost considerations should not guide the use of intrapleural therapy with fibrinolytics and DNase over a primary surgical approach (ungraded recommendation).

Literature review

A cost-effectiveness analysis in health care is an involved process and should ideally include the health-care sector perspective and the societal perspective.[67] Annually, empyema has been reported to affect approximately 80 000 patients in the USA and UK, with costs of approximately US$500 million.[4] The average medication cost of a standard dose of tPA and DNase over 3 days is approximately $7000.[68,69] Such high costs could be prohibitive in some setups. Although various studies have evaluated the effect of intrapleural fibrinolytic and DNase therapy on length of hospital stay and the need for surgical referral, there have been no studies evaluating their cost-effectiveness compared with other management modalities.[5,6,27,38–41,56–58] Median hospital stay in patients with empyema who receive combined intrapleural therapy is approximately 12 days, and the cost per patient is estimated to be €4223.[6,70] Across studies, the mean post-operative length of hospital stay for patients undergoing VATS for stage 2 or 3 empyema ranges from 5 to 17 days.[8,61,66,71–86] An economic evaluation of the MIST2 trial showed that combined tPA and DNase was more cost-effective than were single agents or placebo.[70] These results are not necessarily generalisable to centres across different geographical locations or with varying expertise and availability. Additionally, the MIST2 trial was not designed to detect a difference in health-care costs between groups, and it did not assess patient quality of life via questionnaires. Bouros and colleagues[16] reported that the drug cost of streptokinase (US$180 [SD $47]) was lower than that of urokinase ($320 [SD $123]) at their centre in Greece where the study was done. However, this cost was not comprehensively investigated as part of the overall cost of the hospitalisation. Although a paediatric study has shown primary operative management to be associated with lower hospital costs than non-operative management, studies have not compared it with an approach involving combined intrapleural fibrinolytic and DNase therapy.[87]

Rationale for recommendations

The overall cost-effectiveness of intrapleural fibrinolytic and DNase therapy can be affected by duration of hospitalisation, drug costs, primary procedure costs, the need for secondary procedure(s), costs related to the secondary procedure(s), and costs borne due to complications related to the intervention and during hospitalisation, among other factors. Additionally, to assist decision makers in selecting between different interventions, analysis of costs per quality-adjusted life-years is typically recommended. A definitive study that is designed to provide a thorough economic evaluation of intrapleural fibrinolytic and DNase therapy is warranted to assess its cost-effectiveness compared with other therapies and surgery. However, the differences in costs of hospitalisations, medications, and surgeries across health-care systems in different countries might limit the generalisability of the findings.

Question 11

In adult patients with empyema, should pleural irrigation therapy with normal saline be used in addition to antibiotics and tube thoracostomy?

Recommendations

We suggest that pleural irrigation therapy with normal saline should be considered only in patients who have contraindications to intrapleural fibrinolytic therapy and are not surgical candidates, as assessed by a thoracic surgeon (GRADE 2C).

Literature review

Large-volume intrapleural saline irrigation therapy represents a potential, inexpensive alternative to intrapleural fibrinolytic and DNase therapy in patients with empyema. Such therapy might improve clinical outcomes through dilution and washout of infected material and inflammatory mediators, and by disrupting septations. This technique has been used in various European centres, with a few case series indicating potential benefit.[88–91] Hooper and colleagues[33] did a pilot study of 35 patients with empyema who had a chest tube and randomly assigned them to either standard drainage (with 30 mL saline flushes, three times a day) or pleural irrigation therapy (250 mL of saline irrigation through the chest tube by use of gravity, three times a day) for 3 days. Patients who received pleural irrigation therapy had a greater reduction of pleural fluid, as noted on chest CT at day 3, than did those receiving standard drainage (32·3% reduction *vs* 15·3% reduction; p<0·04). Patients in the pleural irrigation group also required fewer surgical interventions (11% *vs* 47%; p=0·03); however, no

Search strategy and selection criteria

We searched Medline (PubMed interface), Google, and Google Scholar on May 17, 2020, for studies published between Jan 1, 1990, and May 16, 2020. The search strategy comprised controlled vocabulary, such as the National Library of Medicine's MeSH, employing the keywords ((“empyema” OR “parapneumonic effusion” OR “parapneumonic infection” OR “pleural infection) AND (“fibrinolytic” OR “tpa” OR “tissue plasminogen activator” OR “streptokinase” OR “urokinase” OR “dnase” OR “deoxyribonuclease” OR “intrapleural therapy” OR “vats” OR “video assisted thoracic surgery” OR “thoracotomy” OR “surgery” OR “pleural irrigation” OR anticoagulation” OR “coagulopathy”)). We applied no language restrictions. We analysed the reference lists of all identified articles to detect additional articles. A total of 8939 studies were returned. We evaluated relevant studies involving adult patients on the basis of the predefined questions. A total of 83 articles were included in our final assessment and recommendations.

mortality benefit was observed. No clinically significant adverse events were reported.

Rationale for recommendations

The role of pleural irrigation therapy has been evaluated in only one small, randomised controlled pilot study.[33] Although the study showed improvement in pleural fluid drainage and surgical referral rates, the results must be interpreted with caution because the rate of surgical referral in the control group was significantly higher than that in the placebo group of the MIST2 trial (47% *vs* 16%).[6] Therefore, despite being a cheap and easily available alternative, not enough data exist to currently recommend this treatment over validated alternatives, such as intrapleural fibrinolytic and DNase therapy, or surgery.

Conclusion

This consensus statement on the use of intrapleural fibrinolytic and DNase therapy for the management of empyema is intended to offer guidance in decision making. One of the strengths of this Position Paper is that it represents the opinions and perspectives of experts in pulmonary and thoracic surgery from 20 institutions across five countries. We anticipate considerable progress in the field of empyema in the near future and, therefore, there is likely to be a need to reassess our practice periodically, building on the suggestions and recommendations presented in this Position Paper.

Contributors

UC and AA are principal authors with full access to all of the data in this Position Paper, and take responsibility for the integrity of the data and the accuracy of the data analysis. UC, AA, DF-K, VK, and NMR contributed to the conception and design of the work, data acquisition, data analysis, data interpretation, and drafting of the manuscript. All other authors contributed substantially to the study design, data analysis and interpretation, and writing of the manuscript. All authors contributed to the critical revision of the manuscript for intellectual content and all are responsible for the content of this Position Paper.

Declaration of interests

AM serves as an educational consultant for Boston Scientific and Olympus America, outside of the submitted work. MMW serves as a consultant for Lung Therapeutics, outside of the submitted work. NMR has received consultancy and clinical trial support fees from Rocket Medical UK, Lung Therapeutics USA, and Becton, Dickinson and Company, USA. All other authors declare no competing interests.

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