



2021 exceptional surveillance of lung cancer: diagnosis and management (NICE guideline NG122)

Surveillance report

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Surveillance decision

We will not update the [NICE guideline on lung cancer: diagnosis and management](#).

Background to the 2021 exceptional review

NICE's guideline on lung cancer was first published in 2005 and recommends that pleural aspiration or drainage should be performed in an attempt to relieve the symptoms of a malignant pleural effusion ([recommendation 1.5.7](#)) and patients who benefit symptomatically from aspiration or drainage of fluid should be offered talc pleurodesis for longer-term benefit ([recommendation 1.5.8](#)). This area was outside the scope of updates in 2011 and 2019. However, stakeholder feedback during consultation on the 2019 update, provided by NHS England's Clinic Expert Group for Lung Cancer, indicated that indwelling pleural catheters (IPCs) are now being widely used in the management of malignant pleural effusions. Therefore, [NICE conducted an exceptional review of the guideline in 2019](#) to establish if the recommendations covering management of malignant pleural effusions should be updated.

The 2019 exceptional review considered 10 studies, including a 2016 Cochrane systematic review and network meta-analysis that had published after development of the original guideline. The surveillance review concluded that further evidence synthesis was needed to understand the effectiveness and cost implications associated with IPC use. Therefore, NICE asked the National Institute for Health Research (NIHR) to commission a priority update of the Cochrane systematic review to help clarify the effectiveness of both IPC and other newer management strategies for palliation of malignant pleural effusions. This current surveillance review examined the impact of the [updated Cochrane systematic review on interventions for the management of malignant pleural effusions: a network meta-analysis](#) which was published in April 2020.

The updated Cochrane review and findings

The review examined the following intrapleural interventions, compared with another intervention or placebo: talc poudrage, talc slurry, bleomycin, tetracycline, doxycycline, iodine, C parvum, IPC (both daily drainage and without daily drainage), talc administered via IPC, mitoxantrone, mustine, mepacrine, interferon, triethylenethiophosphoramidate and adriamycin. Any other sclerosants identified were also considered.

Only randomised controlled trials (RCTs) were included. Risk of bias was assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions and certainty of evidence was assessed using GRADE.

The primary outcome of the review was pleurodesis failure rate defined, in order of preference, as:

- need for a repeat pleural procedure to manage recurrence of the effusion, or continued drainage of pleural fluid from an IPC (if applicable);
- evidence of significant pleural fluid re-accumulation on radiological imaging;
- pleurodesis failure in the opinion of the trial investigators.

For studies evaluating IPCs, the authors defined an effective pleurodesis as cessation of pleural fluid drainage or device removal because of cessation of drainage, or both.

Secondary outcomes included:

- Adverse effects and complications due to interventions
- Patient-reported control of breathlessness
- Participants' quality of life and symptom control
- Overall mortality.
- Median survival.
- Duration of inpatient stay in days.
- Patient acceptability of the interventions including the need for repeat invasive pleural intervention.
- Relative costs of the comparative techniques.

Findings were analysed using both direct and indirect (network meta-analysis) treatment comparisons.

New searches were undertaken covering April 2015 to June 2019.

Included studies

The updated Cochrane systematic review and network meta-analysis (NMA) included 80 randomised trials (18 new studies) with 5,507 participants (2,079 new participants).

Across the 80 studies low risk of bias was reported in the following domains: allocation concealment, 42 studies; performance bias, 22 studies; detection bias, 16 studies; attrition bias 61 studies; reporting bias, 69 studies; other bias, 66 studies. Three studies were reported as having low risk of bias in all domains.

The summary findings from the Cochrane review, which are detailed below, cover the most commonly compared interventions with the most widespread availability, based on available evidence: they are talc poudrage, bleomycin, IPC – not daily drainage, doxycycline and placebo, with talc slurry as the main comparator.

Primary outcome

For the primary outcome of pleurodesis failure rate, 55 studies (n=3,758 participants) of 21 interventions were included in the primary NMA.

In comparisons with talc slurry the following summary findings are reported:

- Talc poudrage odds ratio (OR) 0.50; 95% credible interval (Cr-I), 0.21 to 1.02, moderate certainty; (9 RCTs, 530 participants)
- Bleomycin OR 2.24; 95% Cr-I, 0.10 to 4.68, low certainty; (21 RCTs, 528 participants)
- IPC without daily drainage OR 7.6; 95% Cr-I, 2.96 to 20.47, moderate certainty; (6 RCTs, 405 participants)
- Doxycycline OR 2.51; 95% Cr-I, 0.81 to 8.4, low certainty; (5 RCTs, 117 participants)
- Placebo OR 15.9; 95% Cr-I, 3.76 to 79.90, moderate certainty; (4 RCTs, 159 participants).

The anticipated absolute effect, based on data from the primary network, was calculated and indicated:

- 18 (95% Cr-I, 11 to 24) failures out of every 100 participants receiving talc slurry

- 10 (95% Cr-I, 4 to 19) failures out of every 100 participants receiving talc poudrage
- 32 (95% Cr-I, 17 to 52) failures out of every 100 participants receiving bleomycin
- 62 (95% Cr-I, 36 to 82) failures out of every 100 participants receiving IPC without daily drainage
- 77 (95% Cr-I, 42 to 95) failures out of every 100 participants receiving placebo.

The results indicate that talc poudrage and talc slurry are effective methods for achieving a pleurodesis, with lower failure rates than other commonly used methods. Direct, pair-wise meta-analysis results for pleurodesis failure rate were limited to 12 direct comparisons. Results for all direct comparisons are presented in the [direct meta-analysis of pleurodesis failure table in the Cochrane review](#). There were no direct comparisons of talc and IPC with or without daily drainage.

Results for the pleurodesis failure outcome are also provided on the overall ranking of each intervention in the NMA. Talc poudrage and talc slurry ranked 3 (95% Cr-I 1 to 6) and 5 (95% Cr-I 3 to 10), respectively. The interventions which ranked 1 (95% Cr-I 1 to 16) and 2 (95% Cr-I 1 to 11) were thoracoscopic mechanical pleurodesis (TMP) and mistletoe (viscum), respectively. They were, however, only evaluated by very small studies (63 participants randomised to TMP and 10 to mistletoe [viscum] in total), with an overall high risk of bias. The wide Cr-Is and very small number of participants randomised to these interventions make it difficult to draw conclusions about their use in routine clinical practice.

IPCs and pleurodesis failure rate

The NMA indicates that IPC with daily drainage regimen has a higher success rate than IPC without daily drainage (ranked joint 11 versus 18, respectively). Overall, there was limited evidence on IPCs with daily drainage. One study compared talc slurry to daily IPC drainage (OR 0.30; 95% CI 0.08 to 1.14; n= 55). Two studies comparing IPCs without daily drainage to IPCs with daily drainage suggested a higher pleurodesis failure rate in those without daily drainage (OR 3.23; 95% CI 1.79 to 5.85; n=236).

Secondary outcomes

Procedure-related fever, based on NMA: there was little difference between talc slurry and other interventions for procedure-related fever (30 studies, n=2,004):

- talc poudrage: OR 0.89; 95% Cr-I 0.11 to 6.67, low certainty
- bleomycin: OR 2.33; 95% Cr-I 0.45 to 12.50, low certainty
- IPC (not daily drainage): OR 0.41; 95% Cr-I 0.00 to 50.00, low certainty
- doxycycline: OR 0.85; 95% Cr-I 0.05 to 14.29, low certainty.

Procedure-related pain, based on NMA: there was little difference between talc slurry and other interventions (31 studies, n=2,753):

- talc poudrage: OR 1.26; 95% Cr-I 0.45 to 6.04, very low certainty
- bleomycin: OR 2.85; 95% Cr-I 0.78 to 11.53, low certainty
- IPC (not daily drainage): OR 1.3; 95% Cr-I 0.29 to 5.87, low certainty
- doxycycline: OR 3.35; 95% Cr-I 0.64 to 19.72, low certainty.

Overall mortality, based on NMA: there was little difference between talc slurry and other interventions (31 studies, n=2,816):

- talc poudrage: OR 0.87; 95% Cr-I 0.53 to 1.43, very low certainty
- bleomycin: OR 1.03; 95% Cr-I 0.45 to 2.41, low certainty
- IPC (not daily drainage): OR 0.8; 95% Cr-I 0.47 to 1.4, low certainty
- doxycycline: OR 0.7; 95% Cr-I 0.16 to 3.0, very low certainty.

Post-intervention patient-reported control of breathlessness, based on direct comparisons: there was no difference in comparisons of talc slurry with talc poudrage and IPC (4 studies, n=379):

- talc poudrage: mean difference (MD) 4.0; 95% CI -6.26 to 14.26, moderate certainty
- bleomycin: uncertain
- IPC (not daily drainage): MD -6.12; 95% CI -16.32 to 4.08, low certainty
- doxycycline: no direct evidence.

Repeat invasive pleural interventions, based on direct meta-analysis: comparisons with talc slurry summary findings showed (9 studies, n=883):

- talc poudrage: OR 0.96; 95% CI 0.59 to 1.56, moderate certainty
- bleomycin: OR 4.33; 95% CI 0.16 to 114.58, very low certainty
- IPC (not daily drainage): OR 0.25; 95% CI 0.13 to 0.48, moderate certainty
- doxycycline: no direct evidence.

There was no difference between talc slurry and talc poudrage in the risk of requiring a repeat invasive pleural procedure for symptomatic re-accumulation of pleural fluid. In comparison, bleomycin needed more and IPC needed fewer repeat procedures. The anticipated absolute effect, based on the difference between the risk of the intervention group with the risk of the control group, was calculated and indicated that:

- 20 (95% CI, 16 to 24) out of every 100 participants receiving talc slurry require repeat invasive procedures
- 19 (95% CI, 11 to 30) out of every 100 participants receiving talc poudrage require repeat invasive procedures
- 52 (95% CI, 4 to 97) out of every 100 participants receiving bleomycin require repeat invasive procedures
- 6 (95% CI, 3 to 11) out of every 100 participants receiving IPC without daily drainage require repeat invasive procedures.

Quality of life

Based on the findings of 6 studies the review identified improvements in post-intervention quality of life outcomes in participants with IPCs (with or without daily drainage), talc slurry, talc poudrage and doxycycline pleurodesis. There was insufficient comparable data to perform an NMA of quality of life outcomes. Five studies of IPCs reported quality of life outcomes, of those, 2 compared IPC (without daily drainage) to talc slurry and did not identify any difference between the interventions.

Relative costs of interventions

The review identified only limited data regarding the relative costs of many of the interventions, with 7 of 80 trials reporting relative costs. Three studies found talc slurry to be cheaper than bleomycin (these were dated 1997, 2000 and 2004). One study from the

UK reported the cost of VATS pleurectomy was more than talc pleurodesis. Only 1 study conducted a cost-effectiveness analysis, it was from the UK; it found IPCs to be more cost-effective than talc slurry in patients with limited survival, but substantial uncertainty in the estimate was identified.

Equalities

No equalities issues were identified during the surveillance process.

Overall decision

The updated Cochrane review demonstrated that talc poudrage and talc slurry were associated with the lowest pleurodesis failure rates compared with other common interventions for which there is available evidence. In the primary NMA estimated ranks, talc poudrage and talc slurry were third and fifth of 21 interventions. TMP and mistletoe (*viscum*) interventions were ranked joint second and therefore higher than talc slurry, but they were evaluated by small studies and there is low confidence in the findings as a basis for informing practice. The available evidence does not support a change to recommendations, in respect of these 2 interventions.

IPCs with or without daily drainage were associated with higher pleurodesis failure rates than most of the other interventions assessed in the NMA; IPC with daily drainage ranked joint 11 and IPC without daily drainage ranked 18 out of 21 interventions. There was limited evidence on IPCs with daily drainage, although they appear to be more effective than IPCs without a daily drainage regimen in increasing the chance of pleurodesis success. It is plausible that where daily drainage of IPCs can be maintained it would improve the primary outcome of pleurodesis failure.

Regarding adverse effects, there was little difference between talc slurry and other interventions, including IPC, for procedure-related fever or pain. There was also little difference in comparisons of talc slurry with talc poudrage and IPC for patient-reported control of breathlessness. The evidence on mortality also showed little difference between talc slurry and other interventions, including IPC.

The Cochrane review shows that IPC had a higher pleurodesis failure rate compared with talc, but that patients needed fewer further invasive pleural interventions. IPC may therefore be appropriate for patients where it is desirable to avoid or reduce subsequent

invasive pleural interventions and pleurodesis failure is less important. Adverse effects are likely to be similar when comparing the 2 approaches, but an area of uncertainty is effect of daily drainage as most studies reported on IPC without daily drainage.

Treatment choice will require balancing which option is appropriate for patients, with IPC management shifting the burden of care to the community, patients and their carers. No studies from the Cochrane review reported on the patient burden of community IPC drainages and impact this may have on quality of life.

In the absence of further research to clarify the key outcomes and costs, particularly for IPC with daily drainage, the new evidence does not have an impact on the recommendations. These findings support the current recommendation in the NICE guideline for use of talc to manage pleural effusion and there is no need to update it.

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