

# Comparisons of doxycycline solution with talc slurry for chemical pleurodesis and risk factors for recurrence in South Korean patients with spontaneous pneumothorax

Eun Ha Park,<sup>1,2</sup> Joo Hee Kim,<sup>3,4</sup> Jeong Yee,<sup>4</sup> Jee Eun Chung,<sup>5</sup> Jong Mi Seong,<sup>4</sup> Hyen Oh La,<sup>2,6</sup> Hye sun Gwak<sup>1,4</sup>

<sup>1</sup>Graduate School of Converging Clinical & Public Health, Ewha Womans University, Seoul, Republic of Korea

<sup>2</sup>Department of Pharmacy, the Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, Republic of Korea

<sup>3</sup>College of Pharmacy & Institute of Pharmaceutical Science and Technology, Ajou University, Suwon-si, Republic of Korea

<sup>4</sup>College of Pharmacy & Division of Life and Pharmaceutical Sciences, Ewha Womans University, Seoul, Republic of Korea

<sup>5</sup>College of Pharmacy, Hanyang University, Ansan-si, Republic of Korea

<sup>6</sup>College of Pharmacy, The Catholic University of Korea, Seoul, Republic of Korea

## Correspondence to

Dr Hye sun Gwak, College of Pharmacy & Division of Life and Pharmaceutical Sciences, Ewha Womans University, Seoul 03760, Korea; hsgwak@ewha.ac.kr

EHP and JHK contributed equally.

Received 28 November 2017

Revised 17 March 2018

Accepted 27 March 2018

Published Online First

18 April 2018

EAHP Statement 4: Clinical Pharmacy Services.



**To cite:** Park EH, Kim JH, Yee J, et al. *Eur J Hosp Pharm* 2019;**26**:275–279.

## ABSTRACT

**Purpose** Talc slurry (TS) has been commonly used with high success rates in managing spontaneous pneumothorax (SP), but there were concerns of post-procedural complications. Alternatively, doxycycline solution (DS) was used successfully. This retrospective study aims to compare the effectiveness and safety between talc and doxycycline as a sclerosing agent and to investigate risk factors for recurrence in patients with SP.

**Methods** The review of medical records between January 2011 and December 2014 was conducted on 83 patients with SP who underwent pleurodesis with either TS (n=16) or DS (n=67). Recurrence and complications were compared between the DS and TS groups. Associations between recurrence after DS treatment and various factors were analysed.

**Results** Recurrence was significantly higher in the DS group than in the TS group (P=0.033), whereas complications were higher in the TS group than the DS group: fever was significantly higher in the TS group (P=0.001). Recurrences associated with doxycycline use were found significantly more often in patients with recurrent diagnosis of SP, height/weight  $\geq 3.25$  cm/kg and weight <55 kg.

**Conclusion** Talc was more effective without recurrence compared with doxycycline. Clinically insignificant fever associated with pleurodesis was more common with talc. Low weight, high height to weight ratio and recurrent diagnosis of SP were associated with higher recurrence after doxycycline treatment.

## INTRODUCTION

Pneumothorax is defined as the presence of air (gas) in the pleural space with subsequent lung collapse. Most cases of pneumothorax occur spontaneously but can be triggered by an injury to the lung or chest wall.<sup>1</sup> Primary spontaneous pneumothorax (PSP) is idiopathic and predominantly occurs in tall, thin males between the ages of 10 and 30 years, while secondary spontaneous pneumothorax occurs in older people with lung diseases such as chronic obstructive pulmonary disease (COPD), emphysema, lung infections, malignancies and congenital abnormalities.<sup>1</sup> The majority of SP patients exhibit a sudden onset of chest pain and dyspnea, and the symptoms are more prominent if a large pneumothorax exists.<sup>1</sup> The factors which predispose patients to PSP include male sex, smoking, family history and genetic abnormalities.<sup>1,2</sup>

The management of SP focuses on the elimination of pleural air, cessation of air leak and prevention of recurrences.<sup>3</sup> Therapeutic approaches vary depending on the type and size of pneumothorax, severity of symptoms and the presence of persistent air leaks. Generally, surgical intervention is reserved for cases of recurrent or complicated SP, and chemical pleurodesis may be used as an adjunctive therapy after drainage or surgery.

Chemical pleurodesis refers to a procedure to achieve symphysis of the two pleural layers by inflammation and fibrosis induced from a chemical irritant.<sup>4</sup> Currently, talc as slurry or poudrage is the most frequently used agent because it is inexpensive, widely available and perceived to be effective.<sup>5,6</sup> But it is not always regarded favourably because of the various complications such as severe pain, fever, dyspnea, pneumonitis and acute respiratory distress syndrome.<sup>7</sup> Moreover, the use of talc has been limited due to associated impurities such as asbestos and lack of standardisation of talc preparations in terms of the particle size and the type and amount of contaminants.<sup>8</sup>

Over the past years, several alternatives to talc have been studied, and the efficacy of intrapleural tetracycline has been demonstrated for recurrent pneumothoraces as well as malignant pleural effusions (MPEs).<sup>9</sup> In comparison studies with talc in pneumothorax treatment, tetracycline showed a similar recurrence rate and complication profile (pain and fever) with better cost effectiveness.<sup>10,11</sup> Unfortunately, the parenteral form of tetracycline is no longer available due to manufacturing issues.

Subsequently, doxycycline has been used as a sclerosing agent and appeared to be effective in controlling MPEs with manageable side effects such as pleuritic pain.<sup>12</sup> However, experience with its use in managing a pneumothorax is limited. The comparison data of doxycycline with talc is only available for MPE management, where a larger dose of talc is normally used than for the management of pneumothorax.<sup>13,14</sup> Moreover, risk factors for recurrence after treatment were rarely analysed.

## Aim of the study

We aimed to compare the effectiveness between talc and doxycycline as a sclerosing agent and to investigate risk factors for recurrence in patients with non-MPE as well as MPE.

## ETHICS APPROVAL

The Institutional Review Board of Seoul St. Mary's hospital approved this study and waived the requirement for informed consent due to the retrospective nature of the study with collection of anonymous-subject data (IRB#KC15RIS10124).

## METHOD

## Study population and data collection

Patients were eligible if they had a first episode or recurrence of SP confirmed by chest radiography. Hospital records of SP patients who underwent pleurodesis either with talc slurry (TS) or doxycycline solution (DS) at Seoul St. Mary's hospital between January 2011 and December 2014 were retrospectively analysed. Reviewed demographic characteristics included age, sex, height, weight, smoking history 3 months prior to pleurodesis and SP-related features (type, cause, diagnosis and lesion).

## Pleurodesis process

For the purpose of use within 12 hours of pleurodesis, TS was prepared in the pharmacy aseptic units by adding 100 mL of sterile normal saline to 5 g of talc powder and gently agitating the mixture. Pharmaceutical-grade KP-certified talc powder was sterilised by ethylene oxide. For DS, 500 mg of oral doxycycline tablets was ground into a fine powder and dissolved in 100 mL of sterile normal saline, and the solution was filtered aseptically using 0.22 µm filters to remove undesirable particulate matter.

Pleurodesis was performed by instillation of a sclerosing agent through a chest tube. The chest tube was inserted with the guide of thoracoscopy following topical anaesthesia with lidocaine. All patients received premedication with 5 mg of oral oxycodone, 25 mg of intravenous pethidine and 20 mg of intravenous lidocaine. The chest tube was kept clamped for 2 hours at the proximal portion of the tube near the insertion site. To ensure the contact of sclerosing agents with pleural surfaces, patients were rotated over 2 hours, turning the patient 45 degrees from right to left lateral decubitus positions at 15 min intervals. The chest tube was then unclamped for drainage. For the post-procedural pain, analgesic medications (tramadol and oxycodone) were given as required.

## Assessment of outcomes

The primary endpoint was recurrence, which was defined as patients who had to return to the hospital due to relapse during the study period. The secondary endpoint was toxicity, which included post-procedural complications such as fever over 38°C, chill, thoracic pain (medicated for pain as needed), dyspnea (need of O<sub>2</sub> support due to oxygen saturation below 80%) and nausea/vomiting.

## Statistical analysis

Statistical analysis was conducted with SPSS, version 12.0 (SPSS Inc., Chicago, IL, USA). The P value of <0.05 was considered statistically significant. Continuous variables were compared using the Student's t-test or Mann-Whitney U test. The Chi-square test was used to compare categorical variables. For correlation analysis, all variables that showed significant differences with a P value <0.05 by univariate analysis were included in a multiple logistic regression analysis. Area under receiver operating characteristic (AUROC) was constructed to obtain a proper cut-off level for factors which showed significant effects on primary endpoints.

## RESULTS

Ninety-nine patients underwent the chemical pleurodesis with either TS or DS for management of SP at Seoul St. Mary's hospital during the study period. Sixteen patients who had discontinued

**Table 1** Baseline characteristics of patients receiving talc slurry and doxycycline solution

| Characteristic                                | Talc slurry (n=16, 19%) | Doxycycline sol. (n=67, 81%) | P values |
|---|-------------------------|------------------------------|----------|
| Sex   |                         |                              | 1.000    |
| Male  | 14 (87.5)               | 56 (83.6)                    |          |
| Female  | 2 (12.5)                | 11 (16.4)                    |          |
| Age, yr.                                      | 67.3±14.0               | 48.6±21.5                    | <0.001   |
| Height, cm                                    | 168.2±4.4               | 168.6±7.8                    | 0.858    |
| Weight, kg                                    | 59.3±12.5               | 57.2±11.2                    | 0.524    |
| Height/weight, cm/kg                          | 2.9±0.6                 | 3.0±0.5                      | 0.595    |
| Body mass index, kg/m <sup>2</sup>            | 20.9±4.2                | 20.1±3.3                     | 0.388    |
| Smoking                                       |                         |                              | 0.750    |
| Yes   | 3 (18.8)                | 18 (26.9)                    |          |
| No  | 13 (81.2)               | 49 (73.1)                    |          |
| Type of SP                                    |                         |                              | 0.107    |
| PSP   | 3 (18.8)                | 27 (40.3)                    |          |
| SSP   | 13 (81.3)               | 40 (59.7)                    |          |
| Diagnosis of SP                               |                         |                              | 0.474    |
| Initial                                       | 12 (75.0)               | 44 (65.7)                    |          |
| Recurrent                                     | 4 (25.0)                | 23 (34.3)                    |          |
| Lesion of SP                                  |                         |                              | 0.578    |
| Unilateral                                    | 16 (100.0)              | 62 (92.5)                    |          |
| Bilateral                                     | 0 (0)                   | 5 (7.5)                      |          |
| Prior surgery* during hospital stay           |                         |                              | 0.056    |
| Yes   | 3 (18.8)                | 30 (44.8)                    |          |
| No  | 13 (81.2)               | 37 (55.2)                    |          |
| Repeated instillations of pleurodesing agents |                         |                              | 0.650    |
| Once  | 11 (68.8)               | 42 (62.7)                    |          |
| More than twice                               | 5 (31.2)                | 25 (37.3)                    |          |
| Total amount of pleurodesing agents, mg       | 8437.5±8702.3           | 649.3±474.4                  | –        |
| Total duration of CTD, day                    | 14.0±10.5               | 16.2±20.6                    | 0.681    |
| CTD after pleurodesis, day                    | 7.0±6.9                 | 11.0±17.7                    | 0.381    |

Data are presented as number (%) or mean ±SD.

\*Surgery: VATS (video-assisted thoracoscopic surgery) or thoracotomy. CTD, chest tube drainage; PSP, primary spontaneous pneumothorax; SSP, secondary spontaneous pneumothorax.

treatment (n=2), incomplete data (n=4), received both agents (n=4) or died during admission (n=6) were excluded from the study. A total of 83 patients were included in the study, of whom 16 (19.3%) received TS and 67 (80.7%) received DS. Baseline characteristics of the study population of 83 patients are summarised in table 1. The average age of the study patients was 52.2±21.5 years.

Except for age, the groups were not significantly different. Patients in the DS group were significantly younger than those in the TS group (P<0.001). There were more males than females in each group. With a marginal difference, a higher percentage of patients in the DS group than the TS group received the combination of chemical pleurodesis and surgical intervention during hospitalisation (P=0.056). Pleurodesis was performed with an average of 1.7±1.7 doses of TS (5 g per dose) and 1.7±1.3 doses of DS (500 mg per dose). Total amount of talc and doxycycline used for pleurodesis was 8437.5±8702.3 mg and 649.3±474.4 mg, respectively. Duration of chest tube drainage after pleurodesis was similar in both groups.

As shown in table 2, recurrence was significantly higher in the DS group than in the TS group (P=0.033). On the contrary,

**Table 2** Comparisons of outcomes between talc slurry and doxycycline solution

|                                | Talc slurry<br>(n=16, 19%) | Doxycycline<br>solution<br>(n=67, 81%) | P values |
|--------------------------------|----------------------------|--|----------|
| Air leakage                    |                            |  | 0.615    |
| Yes                            | 2 (12.5)                   | 5 (7.5)                                |          |
| No                             | 14 (87.5)                  | 62 (92.5)                              |          |
| Recurrence                     |                            |  | 0.033    |
| Yes                            | 0 (0)                      | 16 (23.9)                              |          |
| No                             | 16 (100.0)                 | 51 (76.1)                              |          |
| Complication (cases)           |                            |  |          |
| Fever                          | 5 (31.3)                   | 3 (4.5)                                | 0.001    |
| Chill                          | 1 (6.3)                    | 1 (1.5)                                | 0.265    |
| Pain                           | 9 (56.3)                   | 39 (58.2)                              | 0.887    |
| Dyspnea                        | 2 (12.5)                   | 2 (3.0)                                | 0.110    |
| Nausea/vomiting                | 2 (12.5)                   | 3 (4.5)                                | 0.226    |
| Duration of hospital stay, day | 29.2±28.5                  | 19.1±22.7                              | 0.135    |
| Death after discharge          |                            |  | 1.000    |
| Yes                            | 2 (12.5)                   | 7 (10.4)                               |          |
| No                             | 14 (87.5)                  | 60 (89.6)                              |          |

complications were higher in the TS group than in the DS group: fever was significantly higher in the TS group ( $P=0.001$ ).

Recurrences associated with doxycycline use were found significantly more often in patients with the recurrent diagnosis of SP ( $P=0.034$ ). A height/weight ratio higher than 3.25 cm/kg and weight lower than 55 kg were significant factors for recurrence ( $P<0.05$ ) (table 3 and table 4). The cut-off value of height/weight ratio was from the AUROC curve (0.666). On the other hand, the cut-off value of weight was the median value of our study population. Since there was multicollinearity between weight and height/weight, two models were constructed for the multivariate analyses. We constructed two models as shown in table 4. Based on both models, it was found that patients with recurrent diagnosis of SP showed 3.5~4.0 times higher recurrence than those with initial diagnosis of SP. Weight < 55 kg and height/weight  $\geq 3.25$  cm/kg increased recurrence by 4.1 and 5.0 times, respectively.

## DISCUSSION

In clinical practice, chemical pleurodesis has been widely applied in patients with inoperable conditions or those with recurrent pneumothorax after thoracoscopic surgery or chest drainage. Once pleurodesis is indicated, a sclerosing agent is chosen based on its effectiveness and safety profile. In our study, patients with older age received TS rather than DS. TS was probably used on the grounds that age was reported as one of the independent risk factors of recurrence in patients with PSP<sup>15</sup> and major guidelines recommended talc pleurodesis for the management of spontaneous pneumothorax.<sup>16,17</sup> Patients in the DS group, who were younger and more frequently received surgical interventions prior to chemical pleurodesis, which indicated that more aggressive treatment methods were chosen for younger patients.

Since the 1940s, the efficacy of talc pleurodesis in managing pneumothorax has been reported in the literature with 86% to 100% success rates in reducing recurrences. Similarly, none in our TS group had recurrent SP during the follow-up with the usual dose of talc. The efficacy of talc in the treatment of malignant pleural effusion (MPE) has also been well documented in several studies.<sup>18,19</sup>

**Table 3** Variables associated with recurrence in patients with doxycycline

| Variable  | Recurrence         |                   | P values |
|---|--------------------|-------------------|----------|
|   | Yes<br>(n=16, 24%) | No<br>(n=51, 76%) |          |
| Sex   |                    |                   | 0.716    |
| Male  | 13 (81.2)          | 43 (84.3)         |          |
| Female  | 3 (18.8)           | 8 (15.7)          |          |
| Age, year   | 49.6±25.0          | 48.3±20.6         | 0.841    |
| Weight, kg  |                    |                   | 0.039    |
| <55   | 11 (68.8)          | 20 (39.2)         |          |
| ≥55   | 5 (31.3)           | 31 (60.8)         |          |
| Height/weight, cm/kg                                      |                    |                   | 0.007    |
| <3.25   | 6 (37.5)           | 38 (74.5)         |          |
| ≥3.25   | 10 (62.5)          | 13 (25.5)         |          |
| BMI, kg/m <sup>2</sup>                                    |                    |                   | 0.094    |
| <18.5   | 8 (50.0)           | 14 (27.5)         |          |
| ≥18.5   | 8 (50.0)           | 37 (72.5)         |          |
| Smoking   |                    |                   | 0.527    |
| Yes   | 3 (18.8)           | 15 (29.4)         |          |
| No  | 13 (81.2)          | 36 (70.6)         |          |
| Type of SP  |                    |                   | 0.365    |
| PSP   | 8 (50.0)           | 19 (37.3)         |          |
| SSP   | 8 (50.0)           | 32 (62.7)         |          |
| Diagnosis of SP   |                    |                   | 0.034    |
| Initial   | 7 (43.8)           | 37 (72.5)         |          |
| Recurrent   | 9 (56.2)           | 14 (27.5)         |          |
| Lesion of SP  |                    |                   | 1.000    |
| One side  | 15 (93.8)          | 47 (92.2)         |          |
| Both sides  | 1 (6.2)            | 4 (7.8)           |          |
| Prior surgery* during hospital stay                       |                    |                   | 0.068    |
| Yes   | 4 (25.0)           | 26 (51.0)         |          |
| No  | 12 (75.0)          | 25 (49.0)         |          |
| Repeated instillations of pleurodesing agents             |                    |                   | 0.986    |
| Once  | 10 (62.5)          | 32 (62.7)         |          |
| More than twice   | 6 (37.5)           | 19 (37.3)         |          |
| Time between tube insertion and chemical pleurodesis, day | 4.4±5.4            | 5.5±5.6           | 0.516    |

Data are presented as number (%)

\*Surgery: VATS (video-assisted thoracoscopic surgery) or thoracotomy  
CTD, chest tube drainage; PSP, primary spontaneous pneumothorax; SSP, secondary spontaneous pneumothorax

**Table 4** Univariate and multivariate regression analyses to identify predictors for recurrence after doxycycline treatment

| Variable                           | OR (95% CI)                  | Model I<br>AOR (95% CI)     | Model II<br>AOR (95% CI)    |
|------------------------------------|------------------------------|-----------------------------|-----------------------------|
| Diagnosis of SP (recurrent)        | 3.398<br>(1.061 to 10.878)*  | 4.054<br>(1.168 to 14.076)* | 3.486<br>(1.004 to 12.001)* |
| Weight < 55 (kg)                   | 3.410<br>(1.030 to 11.291)*  | 4.053<br>(1.134 to 14.494)* |                             |
| Height/weight, $\geq 3.25$ (cm/kg) | 4.872<br>(1.479 to 16.047)** |                             | 4.970<br>(1.435 to 17.213)* |

For model I construction, diagnosis of SP and weight were included for analysis. For model II construction, diagnosis of SP and height/weight were included for analysis.

\* $p<0.05$ , \*\* $p<0.01$ .

SP, spontaneous pneumothorax, AOR=adjusted OR.

Chemical pleurodesis with doxycycline has been shown to be effective in various settings. In a small study involving patients with pleural effusions and refractory pneumothoraces, 67% of patients receiving 1 g of doxycycline achieved successful pleurodesis.<sup>20</sup> Another prospective study of patients receiving 500 mg or 1 g of doxycycline showed the same response rate (18/27) in patients with MPE or unresolving pneumothoraces.<sup>21</sup> Our patients with SP who were treated with DS pleurodesis showed a similar response with 7.5% of air leaks and 23.9% of recurrence.

In our comparison between talc and doxycycline, talc showed better effectiveness in the recurrence of SP. In contrast, the comparisons of talc with other agents such as minocycline or iodopovidone failed to demonstrate the superiority of talc with statistical significance.<sup>22 23</sup> From the current data, the direct comparison of the effectiveness of talc and doxycycline as a sclerosing agent seems difficult because of a dose-dependent effectiveness<sup>24 25</sup> with no standardised dosing or application technique for the agent. Therefore, the choice between two agents might need additional considerations of complication profile and individual response to the agent.

Several studies have been performed with the purpose of identifying factors associated with recurrent SP following treatment. It is known that recurrent SP mostly occurs within the first few years, and that taller men, females, smokers, patients with underlying lung disease and elderly patients aged  $\geq 60$  years are at a higher risk.<sup>15 26</sup>

A retrospective analysis of 182 patients treated non-surgically for their first episode of pneumothorax showed that greater height and lower weight were significant factors for predicting a recurrent SP.<sup>26</sup> The presence of underlying lung disease such as COPD, emphysema and tuberculosis was also a relevant factor for recurrence. Other larger retrospective studies of patients with PSP also concluded that increased height/weight ratio, younger age or no use of pleurodesis were associated with higher recurrence following the surgical interventions, but not sex, smoking or body mass index.<sup>27 28</sup> Our analysis showed the relationship between pneumothorax recurrence and a patient's body weight and/or height/weight ratio, but not height, age, sex, smoking history or underlying disease. Since the therapeutic approach was different from the previous studies, whether the treatment methods affected the findings of predicting factors for SP recurrence is not clear. Additionally, our patients were older than those in the aforementioned studies.

The importance of weight as a risk factor in our study may stem from the assumption that weight loss and wasting syndrome from underlying illnesses or older age made patients more prone to the recurrence of pneumothorax. The use of sclerosing agents may yield the benefit of reducing the recurrence of SP, but whether it is more beneficial in tall and/or thin patients remains to be determined. In our study, the cut-off value of height/weight was 3.25 from the AUROC. On the other hand, the cut-off value of weight was 55 kg, which was the median value of our study population.

In terms of safety with chemical pleurodesis, there have been mixed reports about the incidence of respiratory complications associated with talc pleurodesis from none to 33%.<sup>7 29</sup> Moreover, the pathological mechanism of lung injury from talc administration is unknown,<sup>30</sup> and a number of factors might have been related although definite risk factors were not suggested.<sup>7 31 32</sup> The effects of dose or particle size of talc on respiratory complications are still under investigation with conflicting results.<sup>8 33 34</sup> In our study, no complicated respiratory reaction was found, but symptoms of dyspnea occurred in both the TS group and the DS group with rates of 12.5% and 3%, respectively. Although there was inconsistency in serious respiratory events reported in the literature, it is generally accepted that talc pleurodesis can result in respiratory failure,

therefore extra caution in patients with pre-existing conditions is recommended.<sup>7</sup>

Similar to the previous observation,<sup>20</sup> pain and fever were the most common complaints in both groups of our patients. Pain occurred often, probably because the pleurodesis procedure for SP is usually more painful than when treating MPEs.<sup>13</sup> The incidence of fever in the TS group was significantly higher than in the DS group but was manageable with analgesics. It is known that fever is an inflammatory reaction that commonly occurs within 12 hours of a talc pleurodesis that helps to close the pleural space.<sup>35</sup> Multiple complications were more often observed in the TS group than the DS group. Therefore, talc is advised to be used with analgesic agents and appropriate drugs for fever control that do not interfere with inflammatory response.

## CONCLUSION

In conclusion, talc was more effective without recurrence in patients with SP, compared with doxycycline. Considering that there is dose-dependent effectiveness in sclerosing agents, further research is required using a higher dose of doxycycline (1 g). Clinically insignificant fever associated with pleurodesis was more common with talc. Furthermore, weight less than 55 kg and height to weight ratio  $\geq 3.25$  cm/kg in addition to recurrent diagnosis of SP were associated with higher recurrence after doxycycline treatment.

## What this paper adds

### What is already known on this subject

- ▶ Talc is the most frequently used agent for chemical pleurodesis, but it has various complications such as severe pain, fever, dyspnea, pneumonitis and acute respiratory distress syndrome.
- ▶ As an alternative agent to talc, doxycycline has been used as a sclerosing agent and appeared to be effective in controlling malignant pleural effusions with manageable side effects such as pleuritic pain.
- ▶ Experience with doxycycline use in managing a pneumothorax is limited.

### What this study adds

- ▶ Recurrence was significantly higher in pneumothorax patients treated with doxycycline compared with those with talc, whereas complications were higher in the talc group than the doxycycline group.
- ▶ Recurrences associated with doxycycline use were found significantly more often in patients with recurrent diagnosis of spontaneous pneumothorax, height/weight  $\geq 3.25$  cm/kg and weight  $< 55$  kg.

**Contributors** EHP, JHK and HSG made contributions to conception and design. EHP and HOL collected data. JHK, JY, JEC, JMS and HSG analysed and interpreted data. EHP and JHK drafted the manuscript. HSG edited the manuscript and gave final approval of the version to be published. All authors read and approved the final manuscript.

**Funding** This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

© European Association of Hospital Pharmacists (unless otherwise stated in the text of the article) 2019. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

## REFERENCES

- 1 Luh SP. Review: diagnosis and treatment of primary spontaneous pneumothorax. *J Zhejiang Univ Sci B* 2010;11:735–44.
- 2 Noppen M. Spontaneous pneumothorax: epidemiology, pathophysiology and cause. *Eur Respir Rev* 2010;19:217–9.
- 3 How C-H, Hsu H-H, Chen J-S. Chemical pleurodesis for spontaneous pneumothorax. *J Formos Med Assoc* 2013;112:749–55.
- 4 Rodriguez-Panadero F, Montes-Worboys A. Mechanisms of pleurodesis. *Respiration* 2012;83:91–8.
- 5 Mohamed KH, Hassan OA. A new look at an old agent for pleurodesis. *Egypt J Chest Dis Tuberc* 2013;62:617–20.
- 6 How CH, Hsu HH, Chen JS. Chemical pleurodesis for spontaneous pneumothorax. *J Formos Med Assoc* 2013;112:749–55.
- 7 Rehse DH, Aye RW, Florence MG. Respiratory failure following talc pleurodesis. *Am J Surg* 1999;177:437–40.
- 8 Ferrer J, Villarino MA, Tura JM, et al. Talc preparations used for pleurodesis vary markedly from one preparation to another. *Chest* 2001;119:1901–5.
- 9 Lee YC, Baumann MH, Maskell NA, et al. Pleurodesis practice for malignant pleural effusions in five English-speaking countries: survey of pulmonologists. *Chest* 2003;124:2229–38.
- 10 Baranitharan M, Kumar PVS, Suraj KP, et al. A prospective study comparing talc and tetracycline pleurodesis in pneumothorax. *IJHSR* 2015;5:50–7.
- 11 Almind M, Lange P, Viskum K. Spontaneous pneumothorax: comparison of simple drainage, talc pleurodesis, and tetracycline pleurodesis. *Thorax* 1989;44:627–30.
- 12 Månsson T. Treatment of malignant pleural effusion with doxycycline. *ManScand J Infect Dis Suppl.* 1988;53:29–34.
- 13 Rodriguez-Panadero F, Antony VB. Pleurodesis: state of the art. *Eur Respir J* 1997;10:1648–54.
- 14 Kuzdzał J, Śladek K, Wasowski D, et al. Talc powder vs doxycycline in the control of malignant pleural effusion: a prospective, randomized trial. *Med Sci Monit* 2003;9:PI54–9.
- 15 Lippert HL, Lund O, Blegvad S, et al. Independent risk factors for cumulative recurrence rate after first spontaneous pneumothorax. *Eur Respir J* 1991;4:324–31.
- 16 MacDuff A, Arnold A, Harvey J, et al. Management of spontaneous pneumothorax: British Thoracic Society Pleural Disease Guideline 2010. *Thorax* 2010;65:ii18–31.
- 17 Baumann MH, Strange C, Heffner JE, et al. Management of spontaneous pneumothorax: an American College of Chest Physicians Delphi consensus statement. *Chest* 2001;119:590–602.
- 18 Shaw PH, Agarwal R. Pleurodesis for malignant pleural effusions. *Cochrane Database Syst Rev* 2004;1:CD002916.
- 19 Laisaar T, Palmiste V, Vooder T, et al. Life expectancy of patients with malignant pleural effusion treated with video-assisted thoracoscopic talc pleurodesis. *Interact Cardiovasc Thorac Surg* 2006;5:307–10.
- 20 Herrington JD, Gora-Harper ML, Salley RK. Chemical pleurodesis with doxycycline 1 g. *Pharmacotherapy* 1996;16:280–5.
- 21 Heffner JE, Standerfer RJ, Torstveit J, et al. Clinical efficacy of doxycycline for pleurodesis. *Chest* 1994;105:1743–7.
- 22 Ng CK, Ko FW, Chan JW, et al. Minocycline and talc slurry pleurodesis for patients with secondary spontaneous pneumothorax. *Int J Tuberc Lung Dis* 2010;14:1342–6.
- 23 Agarwal R, Paul AS, Aggarwal AN, et al. A randomized controlled trial of the efficacy of cosmetic talc compared with iodopovidone for chemical pleurodesis. *Respirology* 2011;16:1064–9.
- 24 Montes JF, Ferrer J, Villarino MA, et al. Influence of talc dose on extrapleural talc dissemination after talc pleurodesis. *Am J Respir Crit Care Med* 2003;168:348–55.
- 25 Hurewitz AN, Wu CL, Mancuso P, et al. Tetracycline and doxycycline inhibit pleural fluid metalloproteinases: a possible mechanism for chemical pleurodesis. *Chest* 1993;103:1113–7.
- 26 Guo Y, Xie C, Rodriguez RM, et al. Factors related to recurrence of spontaneous pneumothorax. *Respirology* 2005;10:378–84.
- 27 Jk Y, Lee SK, Seo HJ, et al. Risk factors for recurrent pneumothorax after primary spontaneous pneumothorax. *Korean J Thorac Cardiovasc Surg* 2008;41:724–8.
- 28 Huang H, Ji H, Tian H. Risk factors for recurrence of primary spontaneous pneumothorax after thoracoscopic surgery. *Biosci Trends* 2015;9:193–7.
- 29 Janssen JP, Collier G, Astoul P, et al. Safety of pleurodesis with talc poudrage in malignant pleural effusion: a prospective cohort study. *Lancet* 2007;369:1535–9.
- 30 Light RW. Diseases of the pleura: the use of talc for pleurodesis. *Curr Opin Pulm Med* 2000;6:255–8.
- 31 Campos JR, Werebe EC, Vargas FS, et al. Respiratory failure due to insufflated talc. *Lancet* 1997;349:251–2.
- 32 Light RW. Talc for pleurodesis? *Chest* 2002;122:1506–8.
- 33 Genofre EH, Marchi E, Vargas FS. Inflammation and clinical repercussions of pleurodesis induced by intrapleural talc administration. *Clinics* 2007;62:627–34.
- 34 Rossi VF, Vargas FS, Marchi E, et al. Acute inflammatory response secondary to intrapleural administration of two types of talc. *Eur Respir J* 2010;35:396–401.
- 35 Ukale V, Agrenius V, Widström O, et al. Inflammatory parameters after pleurodesis in recurrent malignant pleural effusions and their predictive value. *Respir Med* 2004;98:1166–72.