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50 Abbreviations list:  
51 df = degrees of freedom  
52 IPC = indwelling pleural catheter  
53 IQR = interquartile range  
54 MPE = malignant pleural effusion

55 PS = performance status  
56 SD = standard deviation  
57  
58

## 59 **Abstract**

### 60 Background

61 Indwelling pleural catheters (IPC) offer an alternative to talc pleurodesis in recurrent effusion, especially in  
62 patients wishing to avoid hospitalisation. Two randomised trials have demonstrated reduced time in hospi-  
63 tal using IPCs versus talc pleurodesis in malignant pleural effusion (MPE)—however, the impact of IPCs on  
64 hospital services and patients has not been well studied.

### 66 Objectives

67 To analyse long-term outcomes of IPCs, and understand the hospital burden in terms of requirement for  
68 hospital visits and contacts with healthcare, while the IPC was in situ.

### 70 Methods

71 IPC insertions in a tertiary pleural centre were analysed retrospectively. Reviews of patients with IPCs in  
72 situ considered “additional” to routine clinical follow-up were defined pre-hoc.

### 74 Results

75 202 cases were analysed: 89.6% MPE group ( $n=181$ ), 10.4% non-MPE group ( $n=21$ ). There were a median  
76 3.0 (IQR 3) and 2.0 (IQR 2) ipsilateral pleural procedures prior to each IPC insertion in non-MPE and MPE  
77 groups respectively ( $p=0.26$ ), and a mean 1.3 (SD 1.7) planned IPC-related outpatient follow up visits per  
78 patient. There were 2 (9.5%) and 14 (7.7%) IPC-related infections in non-MPE and MPE groups respectively.  
79 Four (19.0%) and 44 (24.3%) patients required additional IPC-related reviews in non-MPE and MPE groups  
80 respectively ( $p=0.6$ ), and these occurred within 250 days post IPC insertion.

### 82 Conclusions

83 Although IPCs decrease initial length of hospital stay compared to talc pleurodesis via chest drain, IPCs are  
84 associated with significant hospital-visit burden, in addition to planned visits and regular home IPC drainag-  
85 es. IPC-using services need to be prepared for this additional work to run an IPC service effectively.

## Introduction

Pleural effusions are common, with malignant pleural effusion (MPE) the commonest cause of recurrent exudative pleural effusion. Indwelling pleural catheters (IPC) offer an alternative to talc pleurodesis for control of recurrent effusion. Since published randomised data demonstrated similar symptomatic improvement using IPC or talc pleurodesis in MPE,[1] standard practice in the Oxford Pleural Unit is to offer patients a choice between talc pleurodesis and IPC insertion. Two randomised trials demonstrated that IPCs avoid hospital stay in MPE, and are therefore an increasingly attractive option for patients wishing to avoid hospitalisation.[1,2] However, there is a lack of evidence about the overall impact of IPCs on patients and hospital visits beyond the initial insertion procedure done as a day case procedure, and usual scheduled outpatient visits. This study was designed to perform an analysis of the hospital burden after IPC insertion to assess the long-term outcomes of IPC insertion, both for patients and for healthcare organisations.

## Aim

To analyse the long-term outcomes of IPC insertions, and understand the hospital burden in terms of requirement for hospital visits and contacts with healthcare, including unexpected visits, while the IPC was in situ in a real life setting.

## Method

All pleural procedures are recorded in a database in the Oxford Pleural Unit, and all IPC insertion records between 2008 and April 2017 were analysed retrospectively. Data on underlying diagnoses for the pleural effusions, previous ipsilateral pleural procedures performed prior to the IPC insertion, details about IPC insertion, outcomes and complications were collected from the medical records.

Additional data was collected on clinical review requirements, including elective IPC-related outpatient pleural clinic follow up visits, and additional IPC-related patient reviews. 'Additional IPC-related reviews' were pre-hoc defined as reviews at hospital on a pleural procedure list for patients with an IPC in situ, with an IPC-related issue. It is normal practice in our centre to schedule patients with an IPC-related issue for review during a pleural intervention list, allowing any required procedures to be performed on the same day, be it flushing, aspiration, removal or replacement of the drain. This was apart from elective outpatient pleural clinic reviews of patients with an IPC in situ. Scheduled pleural intervention list time for a patient for IPC removal was not considered as an additional IPC-related review. During the period of this data collection, standard practice in our centre was to advise IPC drainage every 2-3 days until patient was reviewed in pleural clinic at one month after IPC insertion. Patients were offered patient review in clinic every 3-4 months thereafter, with the possibility of the patient or community nurse contacting the pleural team in the event of IPC-related issues occurring in the meantime. Some patients would opt out of regular scheduled pleural clinic visits, choosing instead to contact us if and as necessary.

Patients with evidence of pleural infection at the time of IPC insertion (either biochemically and in combination with clinical suspicion of pleural infection, or frank pus on drainage), and where the case was subsequently treated as pleural infection, were not classified as IPC-related infection.

In non-MPEs, IPCs are associated with lower rates of autopleurodesis, especially in hepatic hydrothorax, and the IPC tends to stay in for longer duration when compared to MPE,[3,4] therefore IPCs in non-MPEs likely have different care needs. In this study, patients were divided into two groups according to known baseline diagnosis - malignant pleural effusion ('MPE group') and non-malignant causes ('non-MPE group').

T- tests and Mann-Whitney U tests were used to compare continuous variables and Chi square tests used to compare categorical variables. A *p* value of less than 0.05 was considered significant. GraphPad PRISM 7 was used to analyse data. Time-to-event analyses were conducted using the Kaplan-Meier method.

Ethics approval and patient consent were not required as this is an audit of practice.

## Results

There were a total of 210 IPC insertions. Eight cases were excluded due to insufficient information on hospital visits after the IPC was inserted (3.8%), therefore 202 cases were analysed in total. In the non-MPE group ( $n=21$ ), median age at IPC insertion was 69.6 years (IQR 5.2) and 28.6% ( $n=6$ ) were female. In the MPE group ( $n=181$ ), median age at IPC insertion was 70.0 years (IQR 18.0) ( $p=0.4$ ) and 48.0% were female ( $n=87$ ) ( $p=0.09$ ,  $\chi^2$  2.88, 2df). The median follow up time for all patients while the IPC was in situ was 84.5 days. The underlying causes for the pleural effusions in the MPE (89.6%,  $n=181$ ), and non-MPE (10.4%,  $n=21$ ) groups are shown in Table 1.

#### Multiple IPC insertions per patient

13 of the 202 IPC insertions (6.4%) were carried out in patients who had already had an IPC previously inserted during the same period, and the reasons for the second IPC insertion were: contralateral recurrent MPE ( $n=10$ ), IPC blockage ( $n=1$ ), previous accidental removal of the IPC ( $n=1$ ), and dislodged IPC catheter tip ( $n=1$ ).

#### Previous pleural procedures

Prior to IPC insertion, there were a total of 51 documented ipsilateral pleural procedures in the non-MPE group (median 3.0 per IPC insertion, IQR 3), and 399 in the MPE group (median 2.0 per IPC insertion, IQR 2) ( $p=0.28$ ). These procedures included pleural aspiration ( $n=18$  in the non-MPE group,  $n=180$  in the MPE group), chest drain insertion ( $n=16$  in the non-MPE group,  $n=95$  in the MPE group), failed talc pleurodesis (slurry or poudrage)  $n=7$  in the non-MPE group,  $n=77$  in the MPE group) and thoracoscopy ( $n=10$  in the non-MPE group,  $n=47$  in the MPE group), excluding those with missing data ( $n=4$  for non-MPE,  $n=13$  for MPE group). There was one patient with no previous ipsilateral pleural procedures prior to IPC insertion, and this was a patient with previously diagnosed MPE and IPC insertion, who opted for a contralateral IPC insertion when a contralateral enlarging pleural effusion developed.

#### Complications

##### *Infection:*

There were 2 IPC-related infections in the 21 non-MPE patients (9.5%): a soft tissue infection at the IPC insertion site occurring 14 days after IPC insertion, and a pleural space infection occurring 180 days after IPC insertion.

In total, 8.3% ( $n=15$ ) of the MPE group had evidence of pleural infection at the time of IPC insertion (i.e. aspiration of frank pus, or if biochemical and pH analysis of the fluid was compatible with pleural infection in a patient in whom there was also clinical suspicion of pleural infection). Of the remaining 166 patients in the MPE group, 8.4% ( $n=14$ ) had new infection while the IPC was in situ (compared to 2 IPC-related infections in the non-MPE group,  $p=0.9$ ): 2.4% ( $n=4$ ) had soft tissue infection occurring a median 106 (IQR 113.5) days after IPC insertion, and 6.0% ( $n=10$ ) had pleural space infection occurring a median 171.5 (IQR 224.8) days after IPC insertion (Figure 1).

##### *IPC-related clinical review requirement:*

In the non-MPE group there were 4 IPC-related patient reviews: three patients in total, one of whom had 2 reviews. Patient reviews occurred a median 53.5 (IQR 93.8) days after IPC insertion. These included one IPC re-insertion secondary to fall-out, one IPC removal secondary to pleural infection, one peri-catheter leak, and one IPC related soft tissue infection. Procedures conducted included review and thoracic ultrasound only ( $n=2$ ), IPC removal ( $n=1$ ), IPC removal and re-insertion of a new one ( $n=1$ ).

In the MPE group, there were a total of 44 IPC-related patient reviews and procedures (compared to 4 IPC-related reviews for the non-MPE group,  $p=0.6$ ), in addition to regular elective clinic follow ups. These reviews occurred a median 54 (IQR 75.5) after IPC insertion and included 24 patients with 1 review, 4 patients with 2 reviews, and 3 patients with 4 reviews. The reasons for these reviews were decreased IPC output ( $n=24$ ), increased symptoms despite drainage ( $n=5$ ), pain while draining or chest wall pain while IPC in situ ( $n=4$ ), catheter fall out ( $n=2$ ), tip of catheter in a locule of pleural fluid therefore unable to drain all effusion ( $n=1$ ), IPC-related infection ( $n=1$ ), other (unclear reason for review ( $n=5$ ), allergy to IPC plaster ( $n=1$ ), spontaneous IPC rupture in situ ( $n=1$ )). Procedures conducted included 26 thoracic ultrasounds only, 6 thoracic ultrasounds and IPC flush and aspiration, 3 re-insertions of IPC secondary to IPC fall-out or rupture, and 9 others.

Figure 2 shows combined data for the timing of the first required IPC-related reviews in the MPE and non-MPE groups. The majority of reviews occurred within 250 days of IPC insertion.

Overall, in the MPE and non-MPE groups combined, 34 (16.8%) patients required specific review for an IPC-related issue, 26 patients (12.9%) required one additional IPC-related review, and 8 patients (4.0%) required more than one additional IPC-related review. Table 2 shows the comparison between patients who required a review for IPC-related issue while the IPC was in situ, and those who did not require a review. No clear characteristic identified those requiring additional reviews from those who did not. There was no statistically significant difference between patients requiring specific IPC-related review in the non-MPE group and in the MPE group ( $p = 0.7$ ,  $\text{Chi}^2 0.1$ ,  $\text{df } 1.0$ ), and neither was there any statistically significant difference between the underlying causes of effusions ( $p = 0.2$ ,  $\text{Chi}^2 19.0$ ,  $\text{df } 15.0$ ).

In the 8 patients requiring more than one additional IPC-related review, no clear characteristics identified those requiring more than 1 review: Seven patients had MPE (primary sites were breast, mesothelioma ( $n=3$ ), lung, thymic and melanoma), 1 had non-MPE (heart failure related effusion); 6 were males and 2 females; median age at IPC insertion was 69.5 years (IQR 17.5); 5 were right sided IPC insertions, 3 were left sided; Eastern Cooperative Oncology Group performance status (PS) at IPC insertion was not available for 5 of these patients, and in the other 3, the PS was 1, 2, and 3; 2 had prior failed talc pleurodesis; they had 3 ( $n=1$ ), 2 ( $n=1$ ), and 1 ( $n=4$ ) documented previous ipsilateral pleural procedures, and information on previous pleural procedures was not available in the other 2 patients.

#### Elective follow up clinic appointments

Patients were followed up electively in the pleural clinic a mean of 1.3 times (SD 1.7) while the IPC was in situ (the mean number of elective clinic visits per patient was 2.1 for the non-MPE group, 1.2 for the MPE group). Figure 3 shows the number of pleural clinic appointments.

#### IPC removals

Overall, 35.6% ( $n=72$ ) of IPCs inserted were removed, a median of 102 days (IQR 76.8) after IPC insertion. In the 21 patients in the non-MPE group, IPC was removed in 8 patients (38.1%), a median of 91 days (IQR 53) after IPC insertion; while 36.5% ( $n=66$ ) of the MPE group (2 patients were excluded from further analysis because of insufficient information on the exact date of removal, therefore  $n=64$  analysed) ( $p=0.69$ ) had the IPC removed, a median 103 days after IPC insertion (IQR 77). The reasons for IPC removal are shown in Figures 4 and 5.

Assuming that autopleurodesis was the reason for the IPC removal in the patients with no drainage or reduced drainage volume, overall autopleurodesis rate was 23.8% ( $n=5$ ) in the non-MPE group and 33.1% ( $n=60$ ) in MPE ( $p= 0.2$ ).

A summary of the data including the reasons for IPC removal for each group of patients is shown in Figures 4 and 5.

#### Survival post IPC insertion

In the non-MPE group ( $n=21$  IPC insertions in total), 19 patients (90.5%) had one IPC inserted, and 1 had a second insertion due to IPC displacement. 15 (75.0%) had died by May 2017, 4 (20.4%) were still alive and there was insufficient information available about 1 patient. There were therefore a total of 19 non-MPE patients assessed for survival.

In the MPE group, 17 (9.4%) were still alive, a further 5 were excluded because insufficient data was available, and 159 patients were included in the analysis of survival.

In the non-MPE group ( $n=19$ ), mean survival from IPC insertion was 324 days (SD 624.1), as compared to a mean survival of 213.8 days (SD 266.6) ( $p= 0.096$ ) in the MPE group ( $n=159$ ).

## Discussion

To our knowledge, this study is the first to assess the clinical impact of IPC use beyond the insertion and removal of the catheter. IPCs are an attractive option for patients wishing to avoid hospitalisation, however there is a lack of published data on the burden on patients and hospitals including additional hospital visits and patient reviews for IPC-related issues.

Our results demonstrate that 17.1% ( $n=31$ ) of MPE patients require additional specific IPC-related review for assessment with ultrasound / other intervention, and of these 22.6% ( $n=7$ ) required more than one review. These additional IPC-related reviews are apart from the scheduled pleural intervention list appointment for IPC removal because of autopleurodesis. As shown in the Kaplan Meier graph (Figure 2), the majority of these reviews occur within 250 days of IPC insertion. In addition, there is significant requirement for IPC-related outpatient follow-up, with a mean of 1.3 visits per patient.

Frequency of removal of IPC due to decreased drainage was 58% in two retrospective reviews of IPC in MPE,[5,6] although the total follow-up time in these studies was unclear. However, our results show a lower rate of removal due to 'autopleurodesis' (32.2% overall: 33.1% in MPE group, 23.8% in non-MPE group) in line with the placebo arm of the ASAP trial which reported 24% rate of autopleurodesis with standard IPC drainage.[7] Excluding patients with evidence of pleural infection at the time of IPC insertion, our results demonstrate significant infection rates of 8.6% (6.6% for pleural infections, 3.0% for soft tissue infections) over the period of follow up, occurring late. This is similar to the 4.9% IPC-related pleural infection rate reported in an international multicenter trial,[8] but higher than that reported in a systematic review of published literature (2.8% IPC-related empyema rate).[9] Previous data shows that IPC related infections can be treated with oral antibiotics.[8]

IPC use is increasing with the increasing number of high quality clinical studies and randomised trials providing evidence of efficacious use,[1,2] in both malignant and non-malignant disease.[4, 10] While it is now established that in MPE, IPC and talc pleurodesis have similar beneficial effects on important patient outcomes such as breathlessness,[1] the majority of studies have focused on short term, hospital focused outcomes such as hospital stay. This data therefore does not capture the full patient and healthcare associated impact of the use of IPCs. The results from this study demonstrate a significant burden to healthcare and hospitals from the use of IPCs, and suggest the requirement for follow up for 9 months after IPC insertion when there is a higher likelihood of the need for further intervention for IPC-related issues.

Non-malignant pleural effusions are associated with poor prognosis, with up to 50% 1 year mortality.[11] This was reflected in our study, as there was no statistically significant difference in the survival from IPC insertion between the MPE and the non-MPE groups of patients, emphasising the fact that patients with recurrent non-malignant pleural effusions have a poor prognosis.

This study has limitations because of the retrospective design, and missing data in a minority of patients. The number of non-MPE patients undergoing IPC insertion was small compared to MPE patients. However, the aim was to understand the hospital burden from IPC insertion to IPC removal in day-to-day practice, and the data obtained achieved this aim. Information about the number of IPC drainages at home by patients themselves, carers or nurses, and the number of, and reason for, any general practitioner visits and phone calls to the hospital while the IPC was in situ, was not available and we were unable to measure the impact of this important additional burden to patients. It is important not to underestimate the impact of this on both patients and healthcare providers, especially with regards to the community nurse home visits. A patient may refuse an IPC insertion based on the need for several regular nurse home visits, when compared to the potential hospital visits they may require should they have a failed talc pleurodesis attempt. In clinical trials, data is usually captured from a hospital perspective, and the time point when no further drainage is required noted. However, most patients with IPC drain pleural fluid at least 3 times a week, and future research should aim to capture this data to fully understand the home patient impact of IPC use.

## Conclusions

Although IPC insertion may decrease the initial length of hospital stay when compared to chest drain insertion and talc pleurodesis, IPCs carry a significant future hospital visit burden to patients. Our results demonstrate that 17.1% of MPE patients required further specific IPC-related review for assessment with thoracic ultrasound / other pleural intervention, 22.6% of these requiring more than one review. Furthermore, our data may well underestimate the true burden of IPC-related treatment given the lack of patient perspective data, the number of district nurse visits and the related health economics.

The true patient burden of continued IPC use has not been well defined and should now be prospectively measured and compared with patients with chest drain insertions and talc pleurodesis from a true quality of life and patient perspective.

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