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ORIGINAL ARTICLE

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Topical antibiotics prophylaxis for infections of indwelling pleural/peritoneal catheters (TAP-IPC): A pilot study

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Abstract

Background and Objective: Indwelling pleural catheter (IPC) and indwelling peritoneal catheter (IPeC) have established roles in the management of malignant pleural and peritoneal effusions but catheter-related infections remain a major concern. Topical mupirocin prophylaxis has been shown to reduce peritoneal dialysis catheter infections. This study aimed to assess the (i) compatibility of IPC with mupirocin and (ii) feasibility, tolerability and compliance of topical mupirocin prophylaxis in patients with an IPC or IPeC.

Methods: (i) Three preparations of mupirocin were applied onto segments of IPC thrice weekly and examined with scanning electron microscope (SEM) at different time intervals. (ii) Consecutive patients fitted with IPC or IPeC were given topical mupirocin prophylaxis to apply to the catheter exit-site following every drainage/dressing change (at least twice weekly) and followed up for 6 months.

Results: (i) No detectable structural catheter damage was found with mupirocin applied for up to 6 months. (ii) Fifty indwelling catheters were inserted in 48 patients for malignant pleural ($n = 41$) and peritoneal ($n = 9$) effusions. Median follow-up was 121 [median, IQR 19–181] days. All patients tolerated mupirocin well; one patient reported short-term local tenderness. Compliance was excellent with 95.8% of the 989 scheduled doses delivered. Six patients developed catheter-related pleural ($n = 3$), concurrent peritoneal/local ($n = 1$) and skin/tract ($n = 2$) infections from *Streptococcus mitis* (with *Bacillus* species or anaerobes), *Staphylococcus aureus, Klebsiella pneumoniae* and *Pseudomonas aeruginosa.*

Conclusion: This first study of long-term prevention of IPC- or IPeC-related infections found topical mupirocin prophylaxis feasible and well tolerated. Its efficacy warrants future randomized studies.

KEYWORDS
indwelling catheter, infection, mupirocin, pleural, prophylaxis, topical antibiotic

INTRODUCTION

Malignant pleural effusion (MPE) is a common condition with a rising incidence worldwide.[1] Its presence usually signifies advanced malignancy and is associated with poor prognosis.[1,2] The resultant breathlessness is debilitating and remains the focus of MPE management. Published randomized clinical trials (RCTs) have established indwelling pleural catheter (IPC) as one of the first-line management options of MPE.[3–5] Similarly, an indwelling peritoneal catheter (IPeC) is useful in managing recurrent malignant ascites.[6]

Despite being an effective modality, IPC-related infections remain a major concern to clinicians. The incidence of IPC-related infections varied among studies[4,7–14] but was reported to be as high as 25.5%.[15] In the largest multicentre study of 1021 patients with IPCs, *Staphylococcus aureus* was found to be the causative organism in almost half of all IPC-related pleural infections.[14] A recent review of microbiology of IPC-related pleural infections from 11 studies by Sethi et al. also found *S. aureus* to be the most frequently reported organism responsible for these infections.[16] IPC-related infections usually require hospitalisation[14] which, based on

our experience, disrupt oncological treatments and may sometimes require the removal of the catheter or more aggressive interventions to eradicate the infection. To date, there has been no effective strategies that have been tested for the long-term prevention of IPC-related infections.

IPC and IPeC share many similarities with peritoneal dialysis (PD) catheters, including both its use and the concerns for infection. PD catheter-related infections[17–19] are often caused by *S. aureus*[20,21] and may require catheter removal to treat the infection or to prevent recurrence.[22,23] The International Society for Peritoneal Dialysis (ISPD) guidelines recommend daily topical application of mupirocin to the catheter exit-site as prophylaxis.[24,25] This is based on clinical trial findings that topical mupirocin prophylaxis significantly reduced the rates of peritonitis and exit-site infections, especially those attributed to *S. aureus* and other Gram-positive organisms.[26,27]

Whether the same strategy can be extrapolated to prevent IPC-related infections is unknown. Current available evidence highlights *S. aureus* (skin commensal) as the most frequently reported causative organism for IPC-related infections and the potential use of topical mupirocin as a prophylactic measure warrants investigation. We aimed (1) to investigate the compatibility of IPC material with mupirocin ex vivo using scanning electron microscope (SEM) and (2) to determine the feasibility, tolerability and compliance of topical mupirocin prophylaxis in patients fitted with an IPC or IPeC.

SUMMARY AT A GLANCE

Indwelling pleural catheter-related infections remain a major concern for which no long-term preventative strategies exist. Topical antibiotics prophylaxis for infections of indwelling pleural/peritoneal catheters (TAP-IPC) is a pilot study applying regular topical mupirocin as prophylaxis for indwelling pleural/peritoneal catheters ($n = 50$). The treatment regimen was feasible and well-tolerated, and its efficacy will be tested in a randomized trial.

METHODS

Compatibility of IPC with mupirocin using SEM

Three commercially available formulations of mupirocin (all 2%) were tested: the nasal ointment (Medsurge mupirocin nasal ointment®, Beyvers GmbH, Berlin, Germany), ointment (Medicianz mupirocin ointment®, Beyvers GmbH, Berlin, Germany) and cream (Bactroban cream®, GlaxoSmithKline, Victoria, Australia). A total of seven IPCs (Rocket Med, Washington, UK) were used. Each catheter was divided into four segments, measuring 3–4 cm in length. Three of the segments were treated with one of the mupirocin formulations, respectively, three times a week, while one segment (without mupirocin/untreated) was kept as the control, Figure 1.

One IPC was examined at each of the following time points: 2 weeks, 1 month, 2 months and 3 months while three IPCs were examined at 6 months. At each time point, samples (including a control) were rinsed and immersed in 100% ethanol (Rowe Scientific, Perth, Australia) overnight to remove any ointment or cream on the surface of the catheter, after which they were examined for any obvious structural change such as opacification,[28] rupture[29] and ballooning.[30] Samples were then cut into 1 cm length to be mounted on a support stud and were coated with a uniform layer of gold–palladium evaporated in the sputter coater (Polaron E5100, Quorum Technologies Ltd, Lewes, UK) for electrical conductivity and thermal protection. The coated sample studs were examined with SEM (FEI XL30, Eindhoven, The Netherlands) for any microscopic structural alteration (e.g., cracks or lesions)[31] at a range of magnifications up to 200× by an experienced scientist (PF).

Safety and feasibility of topical mupirocin prophylaxis in patients with an indwelling catheter

Consecutive adult patients newly fitted with an IPC or IPeC at our tertiary pleural referral service (Sir Charles Gairdner Hospital [SCGH], Western Australia) were prescribed topical mupirocin cream for prophylaxis as a local quality improvement initiative from November 2021 to October 2022, provided the patient had no history of allergy to mupirocin. Patient demographics and relevant clinical data were collected from medical records (SCGH GEKO approval #46277).

Topical mupirocin 2% cream was prescribed to be applied around the catheter exit-site, covering an area of approximately 3 cm in diameter after every drainage or with dressing changes (at least twice a week). All patients received standard care including the usual education and care of the IPC/IPeC, and their medical care was directed by their attending physicians as per standard practice. All patients, carers and community nursing teams performing home drainages were given educational material on application of mupirocin. Follow-ups were carried out weekly (or monthly following IPC/IPeC removal) via phone calls, or in person if patients were attending hospital visits, for up to 6 months or until death. Management decisions on IPC/IPeC care, including frequency of drainage, and decision on catheter removal was made by the attending clinicians.

During follow-up, information regarding drainage and dressing changes, any potential complications or adverse effects, compliance with mupirocin application and concerns from patients were recorded. Any available pleural/peritoneal fluid culture results and episodes of IPC/IPeC-related infections were also collected.

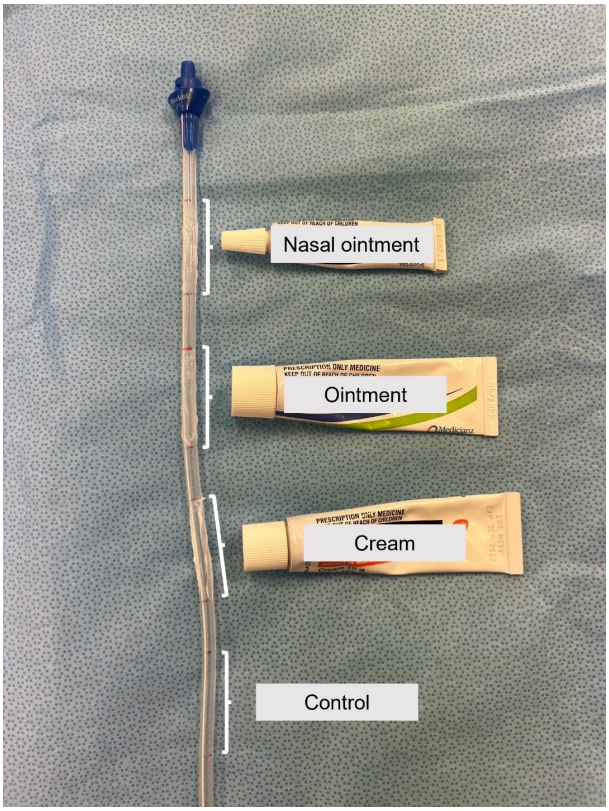

FIGURE 1 An indwelling pleural catheter (IPC) with segments treated with mupirocin nasal ointment, ointment, cream and nothing (control).

TABLE 1 Demographic and clinical characteristics of patients.

Demographic and clinical characteristics	
Sex	
Female, *n* (%)	17 (35.4%)
Age, mean (SD)	70.0 (13.0) years
Primary malignancy causing:	
Malignant pleural effusion ($n = 41$)	
Lung	13 (31.7%)
Mesothelioma	10 (24.4%)
Breast	2 (4.9%)
Others	16 (39.0%)
Malignant peritoneal effusion ($n = 9$)	
Gastric	3 (33.3%)
Colorectal	2 (22.2%)
Others	4 (44.4%)
Comorbidities, *n* (%)	44 (91.7%)
Cardiac disorders (excl. hypertension)	17 (35.4%)
Respiratory disorders	11 (22.9%)
Diabetes mellitus	7 (14.6%)
Neurological disorders	6 (12.5%)
Kidney disorders	3 (6.3%)
ECOG performance status	
0–1	21 (43.8%)
≥2	27 (56.2%)

IPC/IPeC-related local infection was defined as the presence of infectious signs and symptoms including erythema, tenderness, and/or discharge around the catheter exit-site (cellulitis) and/or tunnel tract (tract infection) with or without systemic signs of infection. Erythema and skin irritation occurring where the adhesive dressing material is in contact with the skin without other signs of infection was not defined as an IPC/IPeC-related local infection but a reaction to the dressing material. IPC/IPeC-related pleural/peritoneal infection was defined as the presence of clinical signs and symptoms consistent with pleural/peritoneal infection with the presence of purulent and/or positive Gram stain or culture. Microorganisms isolated from routine culture of pleural fluid of patients are considered colonization if there are no clinical signs/symptoms of infection and the patient did not require treatment with antibiotics. Data were analysed with the GraphPad Prism statistical software (Prism 9.1.0, La Jolla, CA, USA) and results are presented as mean (SD) or median [interquartile range, IQR] as appropriate.

RESULTS

Compatibility of IPC with mupirocin using SEM

A total of seven IPCs, each with segments treated with mupirocin nasal ointment, ointment, cream and nothing (control) were examined. All segments treated with mupirocin ($n = 21$) showed similar appearances to the controls at all time points. No structural changes (e.g., opacification, rupture or ballooning) of the catheters were observed on visual inspection. No cracks or lesions on the catheter surface were detected under the SEM. Longitudinal line patterns resembling repetitive smearing action from mupirocin application were observed on the surface of some segments ($n = 12$), including the control, with no clear pattern of association with the length of time of application.

Patient and clinical characteristics

Forty-eight patients (35.4% female; mean age 70.0 years) had 50 indwelling catheters inserted for malignant pleural ($n = 41$) and peritoneal ($n = 9$) effusions and were prescribed topical mupirocin prophylaxis. Two patients had bilateral insertion of IPCs at different time points and each hemithorax was analysed separately.

The most common underlying malignancies causing pleural and peritoneal effusions were lung (31.7%) and gastric (33.3%) cancers, respectively, Table 1. The majority ($n = 44$, 91.7%) of patients also had multiple significant comorbidities such as cardiac (35.4%) and respiratory (22.9%) disorders. The Eastern Cooperative Oncology Group (ECOG) status was ≥2 in 56.2% of patients.

TABLE 2 Details of mupirocin application.

Total scheduled mupirocin doses (n = 989)	
Doses applied	947 (95.8%)
Missed	42 (4.2%)
Unaware	18 (42.9%)
Forgot	11 (26.2%)
Palliative	5 (11.9%)
Others	8 (19.0%)
Frequency of mupirocin application[a]	
Daily	45 (12.2%)
Three times weekly	55 (14.9%)
Twice weekly	154 (41.7%)
Once weekly	66 (17.9%)
Others	49 (13.3%)
Person applying mupirocin[b]	
Community nurses	296 (80.2%)
Inpatient nurses	60 (16.3%)
Carer	13 (3.5%)

[a]48 patients completed a total of 369 weekly follow-ups. Data represent different frequencies of mupirocin application based on each patient-week.
[b]Data based on 369 patient-weeks.

Twenty-two (45.8%) patients were receiving cancer treatments, including chemotherapy ($n = 15$), immunotherapy ($n = 9$), radiotherapy ($n = 4$), targeted therapy ($n = 3$) and hormonal therapy ($n = 2$), with ten of those patients being on multiple treatments. Fourteen (29.2%) patients were on immunosuppressants.

The median serum white cell count and available serum C-reactive protein (CRP) levels within 24 h prior to IPC/IPeC insertion were 8.34 [6.68–12.49] $\times 10^9$/L and 61 [21–98] mg/L, respectively. Pleural fluids were routinely collected for bacterial culture at the time of indwelling catheter insertion; none grew any organisms.

Mupirocin application and follow-up details

The median duration of follow-up was 121 [19–181] days; 26 (54.2%) patients died within 6 months from disease progression and 20 (40%) IPCs were removed (including 1 dislodged) after a median of 57.5 [36.3–93.8] days upon fluid cessation. In 28 cases (56%), the IPC/IPeCs were in situ at the time of death. One IPC was dislodged after 20 days. At the end of the follow-up period, two IPCs were in situ with ongoing drainage.

Compliance was excellent with 947 of the 989 (95.8%) scheduled doses applied, Table 2. Patients received a median of 14.5 [5.5–26.5] doses of mupirocin and the median time on mupirocin prophylaxis was 38 [20–77] days. Mupirocin was most commonly applied twice weekly (41.7% of cases) and carried out by community nurses (80.2%). Forty-two scheduled doses (4.2%) of mupirocin were not delivered; the most common reasons were unawareness by the attending nurse on the day ($n = 18$) or 'forgotten to apply' ($n = 11$). Missed doses were distributed among 22 patients with the majority of them missing only 1–2 doses, while 26 patients never missed a dose.

Safety of mupirocin application

All patients reported no issues relating to mupirocin application at the IPC/IPeC exit-site, Appendix S1 in the Supporting Information. Patients were satisfied with the use of mupirocin for prophylaxis when specifically asked during follow-up phone calls or clinic visits. Redness ($n = 7$), itchiness ($n = 6$) and skin irritation ($n = 3$) due to the dressing material which resolved upon changing the dressing type were reported; all were considered unrelated to mupirocin. One patient had local tenderness when mupirocin was applied during the healing phase of the insertion wound.

Infection rates

Six catheters (12%) were complicated with catheter-related infection. These included three pleural infections, one concurrent peritoneal and local infection and two cases of local infections.

Two patients developed pleural infection at 4 weeks after IPC insertion and one after 12 weeks. Their pleural fluid grew mixed *Streptococcus mitis* and *Granulicatella adiacens*, mixed *S. mitis* and *Bacillus* species, and *Klebsiella pneumoniae*, respectively, in the presence of compatible clinical picture of infection/sepsis and significantly raised serum CRP levels of 222, 242 and 160 mg/L, respectively. The patient with *Klebsiella pneumoniae* cultured also had clinical symptoms (i.e., fever, productive cough and shortness of breath) and radiological features of pneumonia. All were successfully treated with antibiotics (two had IV piperacillin/tazobactam and one had oral clindamycin) and two had adjunct intrapleural tPA/DNase therapy. None required surgery or additional drain insertion. All three patients developed post-infection pleurodesis by 2 weeks after the infection.

One patient had an IPeC inserted and developed a low-grade fever (which may be tumour-related) and erythema around the catheter exit-site 2 days after, without signs/symptoms of peritonitis. His CRP was only mildly raised (94 mg/L from a baseline of 60 mg/L). The fluid appeared serous and non-purulent but grew *S. aureus* on repeated samples. He was treated as for peritoneal and skin infections with IV piperacillin/tazobactam.

Two patients had local catheter-related infections; both were clinically well without signs of systemic infections. One had an IPeC inserted and developed erythema and purulent discharge around his catheter exit-site 3 weeks after catheter insertion. The exit-site swab yielded *Pseudomonas aeruginosa* and he had a complete response after a course of oral ciprofloxacin. He continued regular ascites

drainage via the catheter without disruptions. The other patient had an IPC inserted and noticed erythema and tenderness along his catheter tract 4 months after insertion and was prescribed oral ciprofloxacin but switched to clindamycin due to intolerance. He passed away 4 days later from cancer progression.

Colonization

Eight patients had microbes isolated from their surveillance pleural fluid culture during routine clinic follow-up visits; none had clinical suggestions of infection and were not treated. The microbes identified were mixed coagulase negative *Staphylococci*, anaerobes (*Bacillus* species), *Streptococcus mitis*, *Brevibacterium* species, *Corynebacterium* species and *Candida* species.

DISCUSSION

This is the first study to explore the potential use of topical mupirocin to prevent IPC/IPeC-related infections. Our study demonstrated that mupirocin application at the catheter exit-site was feasible with a high compliance rate of 95.8% and was well-tolerated. Additionally, the use of mupirocin did not compromise the structural integrity of the indwelling catheter.

IPC is commonly used in patients with advanced cancer who have significant co-morbidities and are at an increased risk of infection. Research efforts to date have mainly focussed on managing, rather than preventing, catheter-related infections.[7,32] Our study represents the first attempt at investigating a long-term infection prevention strategy using mupirocin. Mupirocin is a topical antibiotic with high level of activity against most Gram-positive organisms such as staphylococci and streptococci, as well as certain Gram-negative organisms. This anti-microbial profile makes mupirocin an attractive option for the setting of indwelling catheter prophylaxis, as Gram-positive organisms, especially *S. aureus* are the predominant causative microbes of IPC-related pleural infections.[14] While there is limited literature on IPC-related cellulitis and tract infections, studies have demonstrated that mupirocin prophylaxis is effective in reducing such infections in the context of PD.[27,33] Resistance to mupirocin is unlikely to be a significant concern given the short median duration of survival of patients with MPE.[2] A study in the context of PD has also reported low mupirocin resistance even after continuous application for up to 7 years.[34]

In our study, we included consecutive patients to ensure a representative sample of patients in everyday practice. Despite the frailty of the patient cohort, where half of all patients died within 6 months of IPC/IPeC insertion, we found that mupirocin prophylaxis was both feasible and well tolerated, with excellent compliance rates. In our experience, patients are aware of the seriousness of catheter-related infections and viewed any potential preventative measures positively, including the simple and quick application of mupirocin. To facilitate the process, we provided educational materials and supply of mupirocin, and informed community nurses following referral. We also reinforced the application of mupirocin at each follow-up and ensured that patients had an adequate supply until their next clinic visit. Previous RCTs have demonstrated that the use of intrapleural talc via IPC and aggressive IPC drainages significantly shorten the duration of IPC in situ, allowing its earlier removal.[35,36] Having adopted these approaches, the duration of IPC in situ for patients are shortened. The relatively short duration of mupirocin prophylaxis in this cohort may have also contributed to the high compliance observed.

Our ex vivo experiment showed no structural damage to the catheters even though there have been occasional reports of such changes in PD catheters when mupirocin was used.[28–30] Mupirocin prophylaxis has been demonstrated to significantly reduce PD infections in several studies,[33,37–40] especially for *S. aureus* infections which were reduced by up to two-thirds.[26] However, as this was a pilot study without a control group, we cannot provide efficacy data. It is worth noting that factors such as duration of IPC in situ, survival rates, insertion techniques or ongoing chemotherapy treatment can contribute to the varied incidence rates of IPC-related infections, as documented in the literature.[4,8,9,12,13] Hence, a randomized trial is needed to determine efficacy.

Additionally, the differences between our patient cohort and those undergoing PD may limit the ability to directly extrapolate the efficacy of mupirocin prophylaxis from PD. Patients with MPE have advanced cancer often accompanied by other co-morbidities and may be receiving cancer treatments (e.g., chemotherapy or immunotherapy) or immunosuppressants, which increases their risk of infections. Besides that, IPC drainages in these patients are carried out much less frequently as compared to PD fluid exchanges, which are usually done three times a day or more and may serve as an irrigation to flush out or reduce bacteria load in the peritoneal space. In our patient cohort, some of the infections were attributed to lung organisms and via the parapneumonic route, unlike PD-related infections which are mostly caused by touch contamination with skin bacteria. While the presence of only one case of *S. aureus* infection with atypical presentation (included to be conservative) and the absence of other infections caused by skin organisms are promising findings, mupirocin prophylaxis is unlikely to cover all potential IPC-related pleural infections. Further research is necessary to evaluate the applicability and potential effectiveness of mupirocin prophylaxis in this patient population.

This study has several limitations. Firstly, the absence of a control group limits the ability to draw further conclusions about the early efficacy of mupirocin prophylaxis. However, our pilot data confirms the feasibility of the protocol which will form the basis of an upcoming randomized trial to determine the efficacy of mupirocin, the Australasian Malignant PLeural Effusion (AMPLE)-4 trial. Secondly, this

study was carried out in a tertiary centre with established protocols for patient referrals to well-trained community nursing services. The value of antibiotic prophylaxis may be different (likely higher) in patients managed under less supervised infrastructure. Thirdly, follow-up data were self-reported by patients and may be subjected to positive bias and lack reliability, although this may have been minimized as mupirocin application was mostly carried out and documented by community nurses. Fourthly, the ISPD guidelines recommend daily application of mupirocin in PD patients, as compared to the minimum frequency of twice weekly in our cohort. It is worth noting that PD patients carry out fluid exchanges more frequently than patients with an IPC. Furthermore, the interpretation of the appearance of the exit-site is subjective and relies on clinician's judgement. We adopted a pragmatic approach to capture only those requiring prescription for antibiotics. Importantly, the diagnosis of serious catheter-related pleural or peritoneal infections that are clinically significant, is typically straightforward. Finally, the microbiology of PD-related peritonitis differs from that observed in the pleural cohort. There may potentially be distinct infection pathways involved in these two contexts.

In conclusion, this study represents the first step towards finding a long-term preventative strategy for IPC-related infections, an area that warrants further exploration. Our findings provide the platform for future randomized trials with sufficient power to determine the efficacy of mupirocin as a prophylactic agent, as well as to provide additional insights into the microorganism coverage of mupirocin in patients with an IPC. If mupirocin is proven to be effective, it could have a significant impact on the quality of life of patients with life-limiting illnesses, as well as for those with benign pleural effusions.

AUTHOR CONTRIBUTIONS

Estee P. M. Lau: Conceptualization (equal); data curation (equal); formal analysis (equal); funding acquisition (supporting); investigation (equal); methodology (equal); project administration (equal); resources (supporting); writing – original draft (equal); writing – review and editing (equal). **Sam Faber:** Project administration (equal); resources (supporting); validation (supporting); writing – review and editing (supporting). **Chloe Charlesworth:** Project administration (equal); resources (equal); writing – review and editing (supporting). **Sue Morey:** Project administration (supporting); resources (equal); writing – review and editing (supporting). **Sona Vekaria:** Project administration (equal); resources (supporting); validation (supporting); writing – review and editing (supporting). **Pierre Filion:** Formal analysis (supporting); investigation (supporting); project administration (supporting); writing – review and editing (supporting). **Aron Chakera:** Conceptualization (equal); formal analysis (supporting); methodology (supporting); supervision (supporting); validation (supporting); visualization (supporting); writing – review and editing (supporting). **Y. C. Gary Lee:** Conceptualization (equal); formal analysis (supporting); funding acquisition (equal); methodology (supporting); project administration (supporting); supervision (equal); validation (equal); writing – original draft (supporting); writing – review and editing (supporting).

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CONFLICT OF INTEREST STATEMENT

Estee P. M. Lau, Sam Faber, Chloe Charlesworth, Sue Morey, Sona Vekaria, Pierre Filion and Aron Chakera have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article. Rocket Med Plc provides drainage kits without charge for patients treated with indwelling pleural catheter enrolled in a randomized clinical trial led by Y. C. Gary Lee.

Gary Lee is an Advisory Board member of Respirology and a co-author of this article. Gary Lee was excluded from all editorial decision-making related to the acceptance of this article for publication.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

HUMAN ETHICS APPROVAL STATEMENT

This study was performed in accordance with the Declaration of Helsinki. This human study was approved by Sir Charles Gairdner Osborne Park Health Care Group Quality Improvement Department—approval: #46277. Adult participant consent was not required because this was an audit of a local quality improvement initiative.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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