# A randomized controlled trial of indwelling pleural catheters versus indwelling pleural catheters plus doxycycline pleurodesis for treatment of malignant pleural effusions

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## 1.0 Objective

This study is designed to obtain preliminary data comparing indwelling pleural catheters (IPCs) versus IPCs plus doxycycline for pleurodesis as treatments for malignant pleural effusions (MPE).

- The primary outcome is time to pleural catheter removal.
- Secondary outcomes include assessment of symptom burden, pleurodesis efficacy, complications, health care resource utilization, need of hospitalization for pain control, pain free days and mortality

## 2.1 Rationale

Malignant Pleural Effusions:

MPEs occur in 7 to 15% of lung cancer cases and complicate the course of many other types of cancer.[1] In the United States, more than 156,000 new cases of MPE occur each year, with 75% of these being caused by lung and breast cancer[1,2] Patients usually present with dyspnea, initially on exertion and later at rest. This results in significant functional impairment and subsequent decrease in quality of life (QOL). Because MPE occurs in patients with advanced cancer, management is palliative, with the goal being to alleviate dyspnea and distress. Successful palliation is dependent on long-term relief of the symptoms that are caused by the MPE and prevention of pleural fluid re-accumulation.

**Treatment Options:**

Options for the management of MPE include (1) intermittent thoracentesis; (2) chest tube drainage followed by pleurodesis; (3) thoracoscopic drainage followed by pleurodesis; or (4) pleurodesis using long-term IPCs. It is useful in this context to identify the components of each management strategy.

The first component is some method of fluid drainage (i.e. thoracentesis or chest tube or catheter). The second component is whether or not a pleurodesis agent is used and if so what type. The pleurodesis agent can be talc or doxycycline or any of a variety of other agents that induce scarring and inflammation in the pleura to essentially prevent fluid recurrence. However, pleurodesis agents are not always utilized – i.e. in the intermittent thoracentesis and IPC strategy no pleurodesis agent is used. The evidence basis for choosing between these alternatives has significant gaps and limitations that are clinically important, since there are few randomized trials and most studies have relatively small sample sizes.

Given these limitations, meta-analysis[3,4] suggested that use of chemical agents for pleurodesis was more effective than nothing, that talc was the most effective agent, and that talc insufflation via thoracoscopy was more effective than talc slurry via chest tube. However talc as a pleurodesis agent is associated with acute respiratory distress syndrome (ARDS) and thoracoscopy requires an inpatient stay of several days. A more recent large phase III intergroup trial suggested that talc insufflation via thoracoscopy was similar in efficacy to talc

slurry via chest tube, but both methods required a prolonged inpatients stay and both had

significant complications including ARDS (8% in the thoracoscopic talc group and 4% in the chest talc group).[5] This led to questions regarding talc's safety, whether delivered by chest tube or thoracoscopy. In addition, the meta-analyses noted above[3,4] did not include IPCs, so how IPCs compare to thoracoscopic pleurodesis is not as well studied.

IPCs (IPCs) were pioneered at M.D. Anderson. They have been shown to be effective in relieving dyspnea and improving QOL.[1,6-8] The main complication is catheter infection, which is fairly uncommon and can usually be treated with outpatient antibiotics. Typically about two thirds of patients with IPCs will eventually have decreased drainage, usually several weeks to months after initial placement. Once drainage is minimal, the IPC is typically removed. This is done according to a standard management algorithm. Once removed, the fluid usually does not recur. Of note, IPCs management strategies have not typically involved the use of any pleurodesis agent, but rather pleurodesis is achieved "spontaneously" after prolonged drainage. In addition IPC's allow patients to be treated completely in the outpatient setting, which is a significant advantage compared to thoracoscopic and chest tube pleurodesis techniques. A recent randomized controlled trial of IPCs vs. chest tubes with talc slurry found no significant difference in terms of dyspnea relief at 42 days between the two groups, but dyspnea relief was better at 6 months in the IPC group.[9] However, current evidence based guidelines are not definitive as to which approach is best.[1]

As a result, based on the limited clinical evidence available, IPCs are now the dominant therapeutic option employed for management of MPE at MD Anderson. However, because of the absence of well-designed randomized clinical trials, little consensus exists at the national and international level as to the best procedure and as a result there is significant practice variation.[10,11] For example, a survey of physician practice patterns demonstrated that the first-choice treatment of MPE in the community was chest tubes 75% of the time, video-assisted thoracoscopy 17% of the time, and medical thoracoscopy 8% of the time.[10] In contrast, at M.D. Anderson, over 90% of outpatients receive IPCs, while inpatients may be treated with either thoracoscopy or indwelling catheters. The existence of this widespread variation is cause for concern because the different techniques probably vary in terms of effectiveness, risk, and cost.

**Rationale and Significance:**

In this context it is useful to quantify what the MDACC current standard of care is and how it performs, since that will be the comparator for this study. In this study the intervention will be IPC plus pleurodesis agent (doxycycline) and the comparator is the current standard of care, which is IPC alone. IPC performance has already been studied by our group previously.[8] In a study of 266 patients undergoing IPC placement for MPE at MDACC, using a competing risk model, we found the 1-year cumulative incidence of events was: death with IPC in place, 35.7%; IPC removal due to decreased drainage, 51.9%; and IPC removal due to complications, 7.3%. Recurrent MPE requiring repeat intervention occurred in 14% of patients whose IPC was removed. Fluid recurrence was more likely if the catheter was removed because of complications (e.g. infection) than if it was removed due to decreased drainage (p=0.04).

The proposed study will be the first randomized trial to evaluate the combination of IPCs with a pleurodesis agent vs. conventional IPC management. This combination strategy offers significant potential advantages over existing strategies since it would allow patients with MPE to be managed completely as outpatients (something that cannot be done with chest tubes or thoracoscopic methods) while still allowing patients the benefits of a pleurodesis agent. The pleurodesis agent should shorten the time to pleural space closure, since it will induce more inflammation and fibrosis than conventional IPCs alone. Conventional IPCs (i.e. without any pleurodesis agent) rely upon spontaneous pleurodesis after prolonged drainage but that typically takes 2-4 months and it does not always occur.

We hypothesize that addition of a pleurodesis agent will allow earlier catheter removal. The benefit of earlier catheter removal is that it decreases the risk of infectious complications and saves money since each pack of drainage bottles costs about $500. It also improves patient QOL.
Our secondary hypothesis is that addition of a pleurodesis agent will decrease the frequency of pleural fluid effusion recurrence requiring intervention in those that have their IPC removed. In our prior prospective observational study this occurred in 14% of cases.

While talc is more effective than doxycycline for pleurodesis, doxycycline does not have any ARDS risk. In addition, since one important goal is to manage patients with MPE completely in the outpatient setting, the risk of patients developing ARDS at home in an unmonitored setting is significant. When ARDS has developed in prior studies of talc pleurodesis, the patients were inpatients. Outcomes might be significantly worse if ARDS developed rapidly in a tenuous cancer patient at home. On balance, since this is a palliative intervention in patients that often have very limited pulmonary reserve, the risks associated with talc due to ARDS therefore outweigh the small marginal benefits in terms of fluid recurrence rates as compared to doxycycline.[3,4] Doxycycline is widely available and has been used before for pleurodesis, so the methods could be easily replicated in other institutions and would potentially change the standard of care.

### 2.2 Hypothesis

**Our hypothesis is that IPCs plus doxycycline will be superior to IPCs alone in terms of time to catheter removal. Our secondary hypothesis is that IPC plus doxycycline will be superior to IPCs alone in terms of recurrence of effusions requiring drainage after IPC removal.**

### 3.1 Type of Subjects to be studied

Inclusion Criteria:

1) Outpatients with MPE undergoing IPC placement; 2) Age 18 or older; 3) Sufficient mental capacity to answer SF-6D and Borg score questions.

Exclusion Criteria:

1) Patients undergoing pleurodesis for benign disease (e.g., spontaneous pneumothorax); 2) Inability or unwillingness to give informed consent; 3) Inability to perform phone call and clinical follow-up at MDACC; 4) Previous intrapleural therapy for MPE on the same side;
5) Chylous effusions associated with malignant disease; 6) ECOG of 4 and life expectancy $\leq$ 2 weeks; 7) Doxycycline allergy 8) Contraindication to placement of an IPC (e.g., uncorrected coagulopathy)..

### 4.1 Research Plan and Methods

Study Design:

This is a double blind randomized controlled trial of patients with MPE undergoing IPC placement as part of their standard of care. The Clinical Oncology Research System (CORe) will be used to generate randomization. This will be done immediately after the subject has consented for the protocol.

The primary outcome will be time to pleural catheter removal. Secondary outcomes will include recurrence of effusion requiring drainage in patients that have their IPC removed. Other secondary outcomes will be quality adjusted survival (calculated using the SF-6D to determine utiles and then integrating utiles over time to arrive at quality-adjusted survival), change in

dyspnea (using the Borg score), IPC complications, procedure associated pain, and need for hospitalization due to pain from pleurodesis.[12]

Study Procedures:

The study will prospectively enroll patients being treated for MPE as part of their standard medical care. Note that all measurements are currently part of the standard of care. This includes measurements of QOL, which are captured on the SF-6D for all patients who come to pulmonary clinic. A total of 250 patients undergoing IPC treatment for MPE will be enrolled and randomized in a 1:1 ratio to either IPC + doxycycline or IPC alone. Following enrollment, the schedule of events will be as shown in Figure 1 below. We will obtain informed consent on all patients.

The study will be blinded to the patient and the long term clinical care management team. After initial consent at the time of IPC placement, research coordinators will arrange for a single extra visit to be made at day 5 +/- 2 for all patients. The reason for the 5 +/- 2 days is to allow patients to come during regular clinic hours rather than on weekends. During this additional visit a different physician team, called the pleurodesis team, will give patients either doxycycline or saline control via the IPC. This team is different than the team that will be making all clinical management decisions. The pleurodesis team will only be giving the drugs on day 5 and managing perioperative pain. In this way all management decisions as to catheter removal, complications, and other aspects of pleural effusion care will be made by the standard clinical care team who will be blinded as to the patient's study status. Patients that receive intrapleural pleurodesis agents, whether it is talc or doxycycline or other agents, sometimes have significant pain during the procedure. The standard of care is to control this with short acting narcotics. But we need to keep the management team blinded as to the use of these narcotics since that might bias their decision making.

A standardized pain control algorithm, developed in conjunction with the pain clinic, will be used. This is shown in figure 2 and this will be used by the pleurodesis team in conjunction with the pain management clinic in the perioperative period to control pain. We will assess pain using a VAS as well.

Subsequent visits will follow the current standard of care algorithms. This dictates how often the catheter is drained and when the catheter is removed and how infections and complications are dealt with. These are all in our current care pathways and will be carried out by the usual clinical team. These are shown in figures 3-5 and cover routine drainage (figure 3), malfunctions (figure 4), and infections (figure 5). Research coordinators will capture this data and do phone call follow-up after the catheters are removed in order to determine if fluid recurs. Patients will be followed for at least 1 year after IPC placement.

**Data Collection and Confidentiality Procedures:**

The data will be kept in a database on a password-protected computer in a secure office. This information will only be accessible to the study investigators and staff.

**Statistical Considerations:**

All statistical analyses will be performed in collaboration with Dr. Liang Li from the Department of Biostatistics. Our system of analysis will be to build a composite picture of patients with MPE in order to examine how the intervention affects outcome. We will look at 1) time to catheter removal; 2) time to symptomatic fluid recurrence following IPC removal; 3) quality adjusted survival; 4) dyspnea; and 5) pain free days, the need of hospitalization for pain control and mortality.

The primary outcomes of interest will be time to catheter removal. In our prior study, 148 of the 266 patients undergoing IPC eventually had their catheter removed (56%, 95% CI 49%-62%).[8] This outcome will be analyzed by cause-specific hazard Cox model with treatment group as a covariate. Whenever a catheter is removed the cause for removal will be documented. For the analysis causes will include removal due to decreased drainage (i.e. as per plan) as well as removal due to complications (e.g. infection, empyema, refractory pain) or other reasons (e.g. catheter plugged but no complication to the patient, patient preference without a complication). We know from our prior study that most removals are due to decreased drainage (86%), complications (10%), or other (4%).[8] Death will be a censored event for the primary analysis. For cause specific removal, other causes of removal will be considered as censored event. We will also analyze time to catheter removal for any cause. For the primary outcome we will also conduct pre-specified secondary analyses to evaluate the effect of pre-installation fluid drainage amount (i.e. how much was being put out from the IPC the day of the procedure) and size of residual effusion as assessed by CXR on time to catheter removal. We will also assess for an interaction between these variables and the effect of doxycycline on the outcome of time to catheter removal.

We hypothesize that for patients with very little drainage (defined as < 150 ml the day of randomization) that also have small effusions, that doxycycline will have less effect on time to catheter removal while in patients with larger amounts of fluid drainage doxycycline will have more effect.

For the primary outcome, assuming a Hazard ratio of 2.0 for time to removal of doxycycline vs. conventional treatment and a 1:1 ratio of IPC + doxycycline: conventional IPC patients, then to have 90% power to detect a difference with a two-sided alpha set at 0.05 will require 48 events in each arm (total events=96). The lower border of the 95% CI for catheter removal from our prior study of IPCs was 49%. So if only 49% of patients have their catheter removed for decreased drainage then this will require 196 patients to be enrolled. If 10% of patients drop out then a total of 218 patients will need to be enrolled to generate the 196 patients that will generate 96 events (i.e. catheter removals). We expect dropout rates to be low based on our prior observational study and because the only difference in the intervention arm is a single visit at day 5. Everything else is standard of care. We will be conservative and enroll 250 patients.

Secondary outcomes for pleural fluid recurrence and quality adjusted survival are really exploratory, since the number of events and the magnitude of the effect are likely to be small. For pleural fluid recurrence following catheter removal, we only expect 14% of patients to develop recurrence requiring drainage. Since we have powered the study to have 96 catheter removals, we expect only 14 patients to have fluid recurrence requiring additional intervention. For the secondary outcome of quality-adjusted survival (measured as QALYs), we expect baseline utility to be approximately 0.6 based on our prior study.[8] In prior multivariate analysis the factors impacting change in utility were chemotherapy or radiation after IPC and severity of baseline dyspnea. Patients with more dyspnea experienced greater improvement in quality adjusted survival since the procedure improved their condition more dramatically. We will use the Kaplan-Meier product-limit method to estimate median QALYs following IPC placement. We will use paired t-test to compare baseline and 1-month Borg scores and utilities. A generalized linear model will be used to evaluate whether other variables have any impact on the pairwise differences between baseline and 1 month.

## Data Safety Monitoring Board

The data safety monitoring board will monitor complications in both arms. Based on prior studies conducted at MDACC, 26 of 266 patients (9.8%, 95% CI 6.5% - 14.0%) had one or more complications related to IPC at some point after placement.[8] Complications included wound site infections (4%), empyema (1%), trapped lung (2%), clogged IPC (3%), dislodgement of the IPC (1%), leakage (0.4%), pain and discomfort (0.4%), kinked IPC (0.4%), and decreased drainage due to sub-pulmonic location (0.4%). We will monitor complications in both arms following randomization (i.e. day 5 onward) to ensure the complications in each arm are not higher than 14% (the upper limit of the 95% CI). It is important to recognize that doxycycline and talc pleurodesis are the two most commonly used sclerosing agents in the United States, so there is a large body of data on doxycycline administered via chest tubes indicating that it is safe. Talc, while more effective, has more risk in terms of ARDS.

In terms of efficacy or futility interim analysis, if efficacy is demonstrated earlier, we will still want to enroll the entire cohort, since the secondary outcomes such as time to fluid recurrence, are exploratory but important, since we will base future power calculations off the exploratory data collected in this study, so it will be worthwhile to collect data on the entire cohort.

With regard to futility, while it is possible the study will not achieve the goal HR of 2.0 for time to removal, a competing risk analysis at MDACC of 266 patients demonstrated the 1-year cumulative incidence of death without catheter removal was 35.7% (95% CI : 29.5% - 42.0%); the 1-year cumulative incidence of catheter removal due to decreased drainage was 51.9% (95%CI: 45.4% - 58.3%); and the 1-year cumulative incidence of catheter removal due to complications or other reason was 7.3% (95% CI: 4.2% - 10.5%).[8] The median time for catheter removal when it was removed due to decreased drainage was 2 months. Typically after chest tube doxycycline installation on inpatients the chest tube is removed within 1 week. We estimate that since we will be giving the doxycycline at day 5 +/-2 after IPC placement, and the next follow up is at day 14 and then routine follow up at day 28, that 65-87% of patients will have pleurodesis in the intervention arm. The 65-87% success rate is the estimated rate for doxycycline chest tube pleurodesis (not IPC which has not been done but they should be similar). So our chances of demonstrating clinical success are high.

However, even if we fail to achieve statistical significance, measurement of the HR will be useful in determining future avenues of work, provided the sample size is large enough. If we were to demonstrate early futility, it would not be the same as proving that doxycycline does not work, and the observed sample size at that time point would be too low and the confidence intervals too wide to draw useful conclusions other than that it was unlikely that the study would succeed. If we complete the study to n=250, we should have a more precise representation of the HR which will allow us to evaluate whether we should a) change the sclerosing agent to something more potent (e.g. talc); b) redo the study as a multicenter study using our new estimated HR from this study; or c) a combination of the above. In addition, it may be that a subset of patients (e.g. those that have persistent fluid drainage on day of randomization>150 ml) will have a benefit, but this will require a larger cohort to look at these subsets.

## Budget

We will seek Research-related patient care clinical charges funding (RPCCC) for the 2 patient visits that are not currently part of our standard of care. Pleurodesis for MPE is covered by all carriers and is part of the standard of care, the only part that is not part of the standard of care is the additional visit which is unnecessary for the control arm if this was the standard of care. All drugs and other aspects would be standard of care. The CPT code would be 99212.

**Figure 1. Study flow chart**

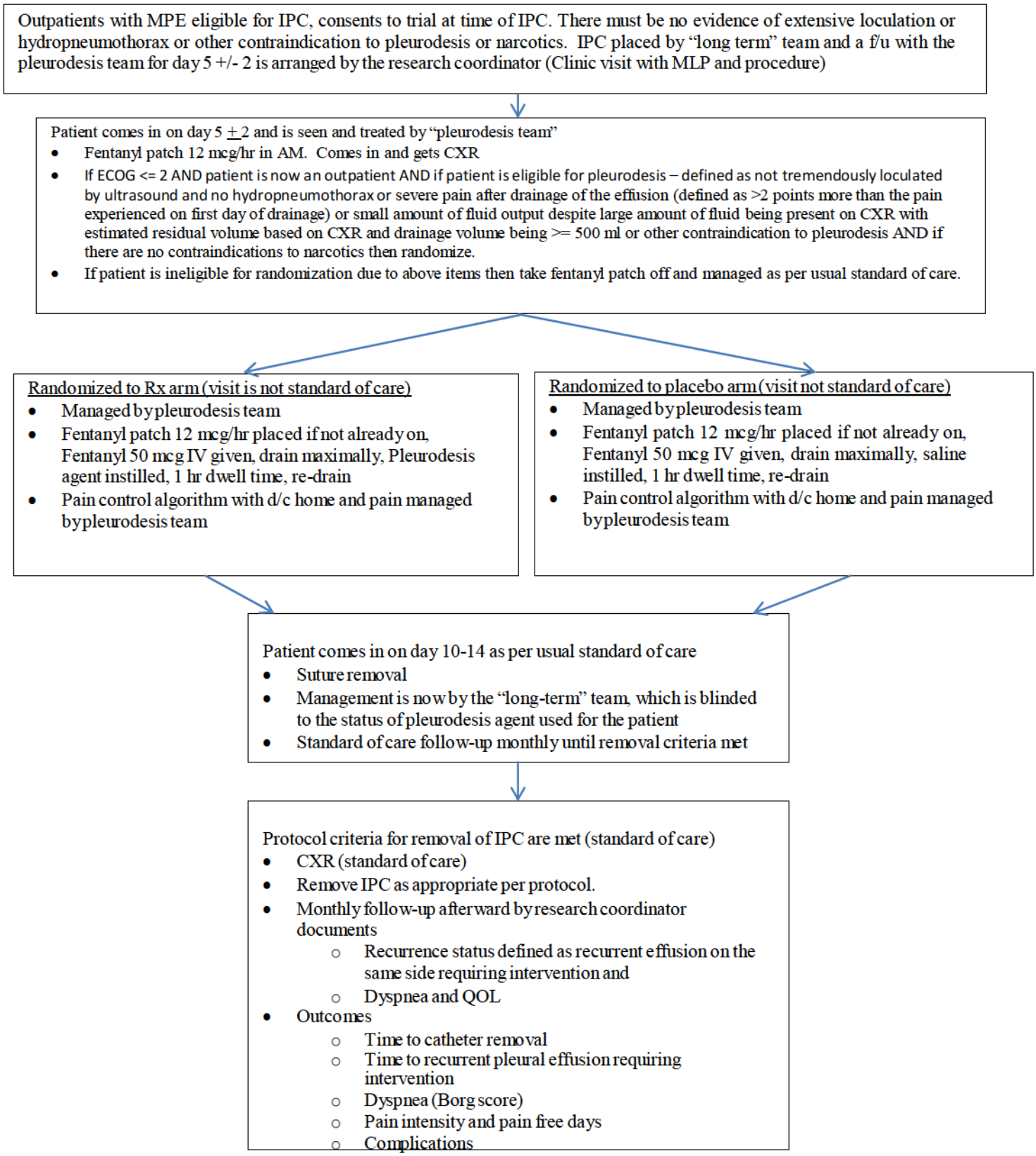


**Figure 2. Pain Control Algorithm for IPC**
**Indwelling pleural catheter pleurodesis Pain Control Algorithm.**

1. Identify patient for IPC with pleurodesis and consent patient. Obtain baseline measures for Borg, SF6D, and pain instrument, as per usual standard. Consent patient for trial if pleurodesis is feasible (i.e. not tremendously loculated effusion and no hydropneumothorax or trapped lung or other contraindication to pleurodesis).
2. If patient consents schedule f/u appointment for day 5 +/- 2 at the time of IPC placement with pleurodesis team. This is a f/u visit with MLP with a procedure slot booked as well for same day (can be booked as IPC)
3. Give them a fentanyl patch 12 mcg/hour to take home. This is to be placed on day 5 +/- 2 ideally in the morning upon waking up prior to f/u appoint since it takes time to have effect
4. Patient comes in for scheduled visit on day 5 +/- 2 for CXR and then to CPC clinic and is assessed by MLP. Baseline SF6D, pain instrument, Borg as per usual standard. Assuming no dramatic change or infection then goes to procedure area. Nurse places IV.
5. Give pain control with Fentanyl 50 mcg at start of IPC procedure
6. Drain pleural fluid as per usual standard of care until pain or cough.
7. Reassess patient and pain control and give one additional dose of fentanyl 25 mcg if pain VAS 5-7 or fentanyl 50 mcg if VAS is 8-10. If pain level on VAS is 0 – 4 no additional fentanyl is needed.
8. Instill pleurodesis agent (e.g. Doxycycline 500 mg dissolved in 50 ml of normal saline + 25 ml of 1% lidocaine (250 mg))
9. Cap for 1 hour, giving additional doses of fentanyl 25 mcg if pain VAS 5-7 or fentanyl 50 mcg if VAS is 8-10. If pain level on VAS is 0 – 4 no additional fentanyl is needed.
10. <u>If pain control is not adequate, defined as a VAS of 7-10, while in the clinic following IPC</u> after fentanyl total dose is 150 mcg or if there is doubt about maintenance of control then patient goes to pain clinic on the 4$^{th}$ floor for walk in appointment prior to discharge. Pulmonary attending or MLP places consult to pain clinic in orders. Pulmonary recovery area nurse is to put in an online consult and calls the pain clinic at 2-1430 to notify them patient is coming gives hand/off sign out. If there are problems regarding availability then nurse can speak to pain clinic supervisor, Angela Jacob. If there is no availability in pain clinic for walk in then the back-up is to send them to EC and have the inpatient pain service come to see as a consult. If this occurs, please place typed note in clinic station using IPC template, delineating need for pain control.
11. <u>If pain control is good,</u> defined as a VAS of 0-4, patient and family receive instruction on pain control algorithm and patient goes home on Hydrocodone 5 mg with acetominophen 325 mg tablets every 4 hours PRN, dispense 28 tablets (7 days) in addition to the fentanyl patch placed previously. Fentanyl patch should be taken off in 3 days. Follow-up care is as per usual IPC protocol.
12. <u>If pain control is inadequate at home</u>, defined as persistent pain (VAS >= 5) despite use of hydrocodone on more than four occasions in a 24 hour period, patient calls in to pulmonary clinic, speaks to clinic nurse. If pain is the issue, she contacts MLP who assesses patient. If pain management does not require pain clinic (i.e. relatively minor),

MLP and pulmonary attending modify regimen, adjust pain meds, and MLP then follows-up by phone at 24 hours after intervention to verify pain is controlled. If pain is still not controlled patient needs to go to pain clinic. Alternatively if pain is too severe at first contact then patient goes straight to pain clinic at MLP/pulmonary attending discretion. MLP notifies attending pulmonary physician and puts in consult for pain clinic at same time. MLP calls pain clinic at 2-1430 to notify them patient is coming and gives hand/off sign out. If there are problems regarding availability then MLP can speak to pain clinic supervisor, Angela Jacob. If there is no availability in pain clinic for walk in then the back-up is to send them to EC and have the inpatient pain service come to see as a consult. If this occurs, please place typed note in clinic station using IPC template, delineating need for pain control so that hand-offs are good. Either way, MLP should document in clinic station with typed or dictated note patient phone encounter, including level of pain (1-10 or VAS), duration, what old pain regimen was (e.g. fentanyl patch 12 mcg/hour and hydrocodone-acetominophen 5-375 one PO QID PRN) and what the change was (e.g. increase hydrocodone-acetominophen to 10-375 one PO QID PRN), and plan for f/u.

13. <u>If patient is overly sedated</u>, patient takes off patch early and does not take hydrocodone and calls pulmonary clinic and speaks to MLP. MLP modifies and reviews with attending. MLP does phone call follow-up at 24 hours to verify that modification of regimen works (i.e. pain controlled and not overly sedated).

Pain Clinic info:
4th Floor
Phone 2-1430
Angela Jacob, supervisor

**Figure 3. Drainage Algorithm of Pleural Fluid after IPC Insertion**

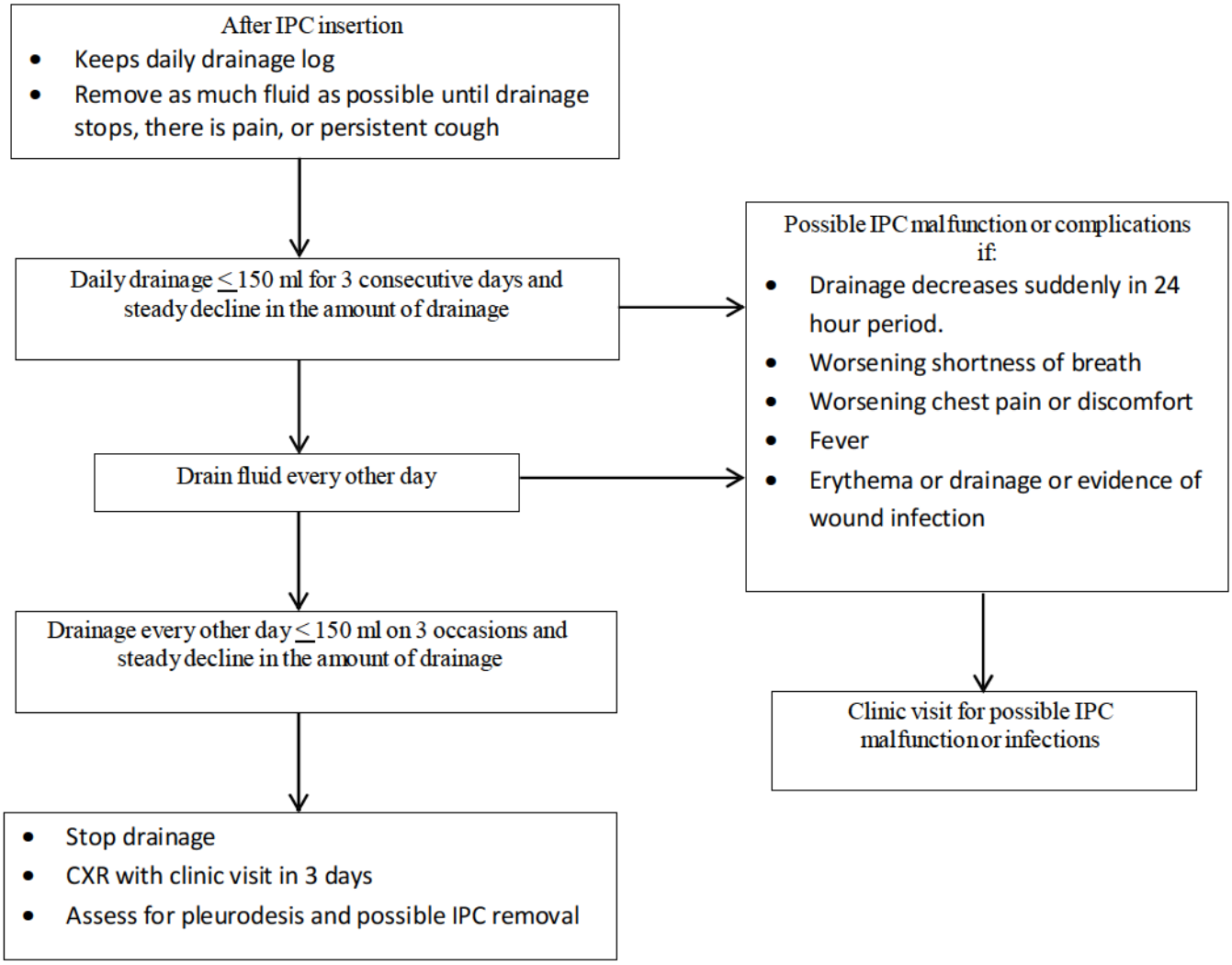


**Figure 4. Management algorithm of IPC malfunctions**

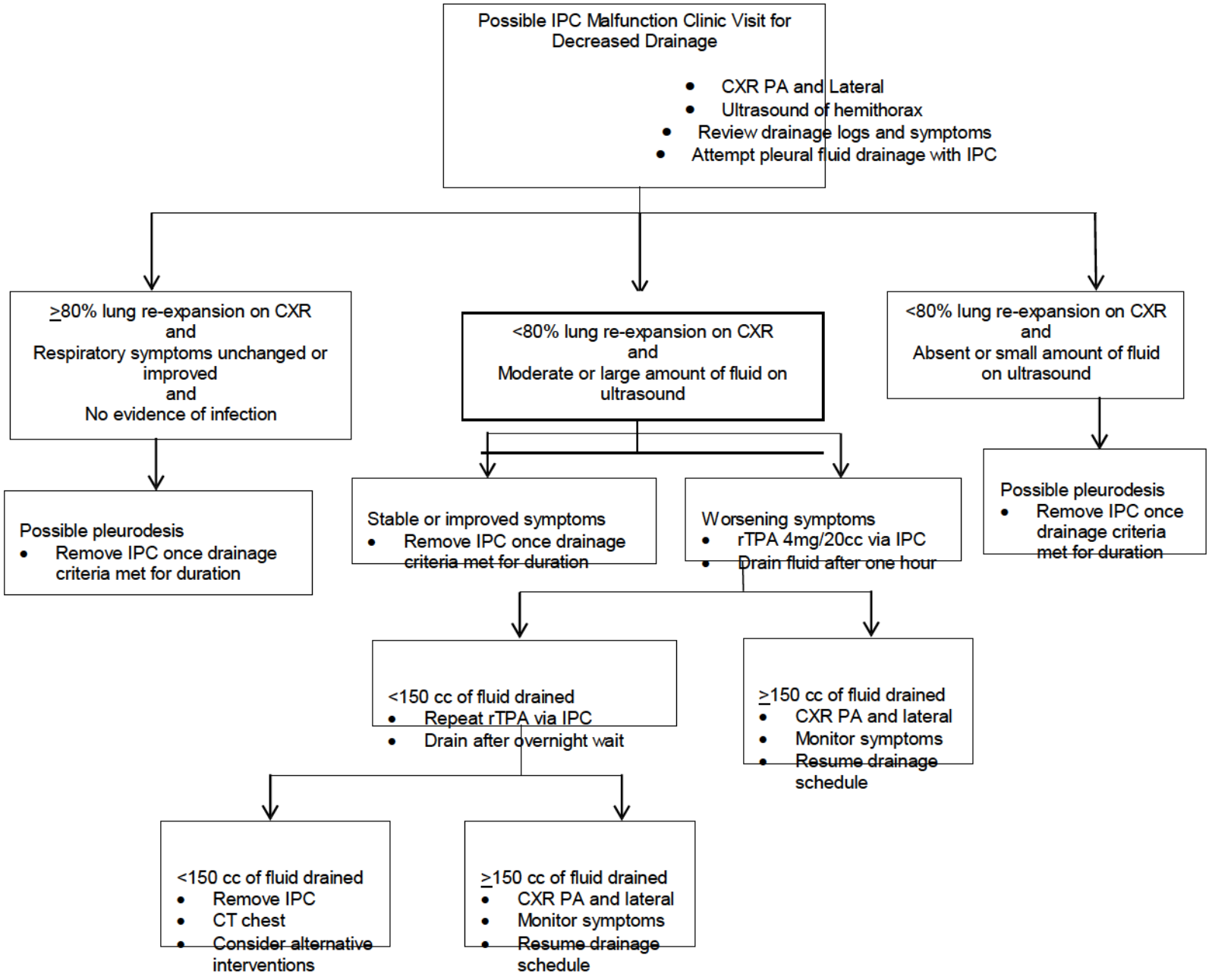
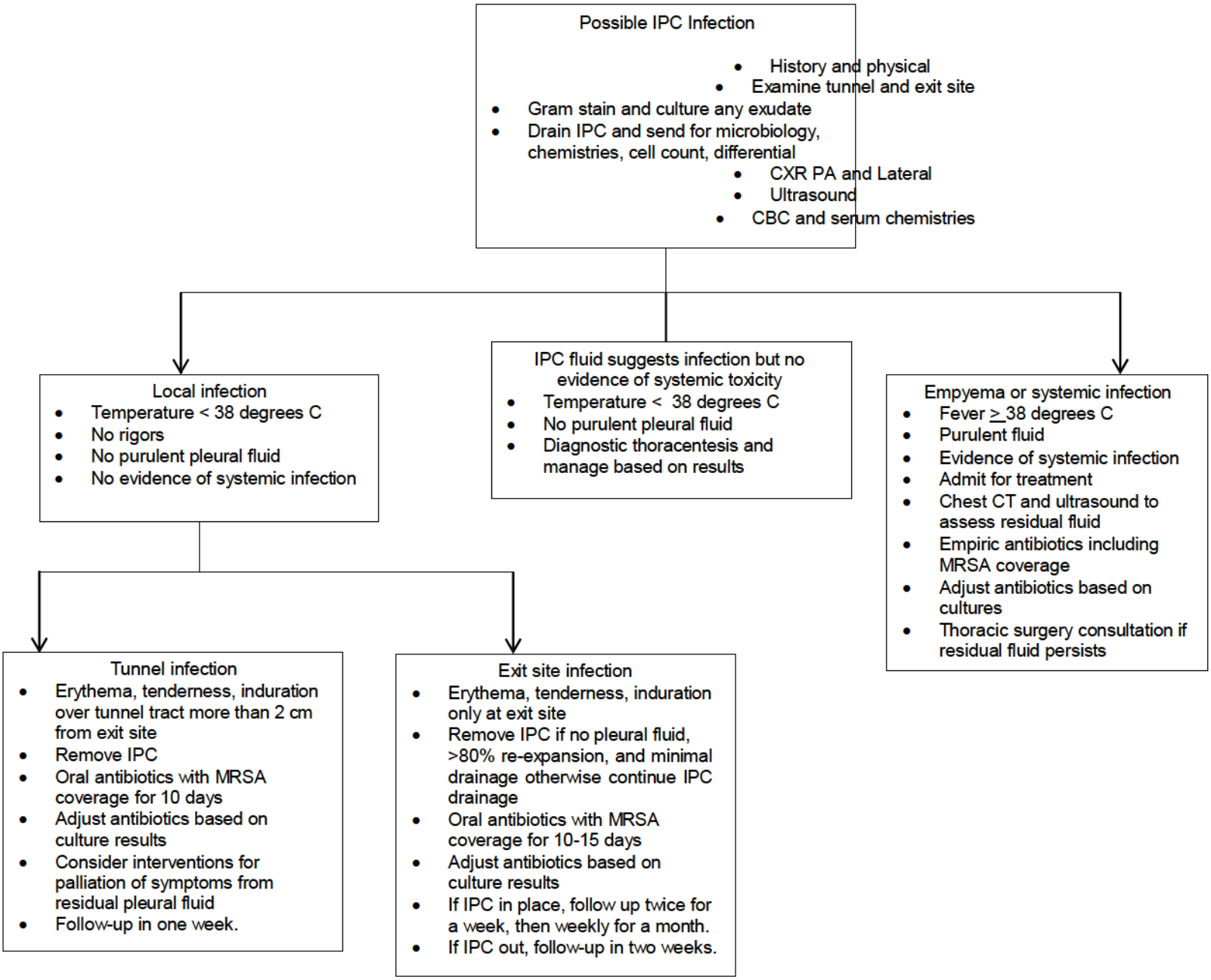


**Figure 5. Management algorithm of possible IPC related infections**



## 5.0 Informed Consent/Authorization

We do plan to consent patients for this randomized controlled study.

## 6.0 References

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