

Outpatient Management of Recurrent Malignant Pleural Effusion and Indwelling Pleural Catheter

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Educational Objectives:

1. Review the rationale for performing outpatient thoracentesis.
2. Understand a stepwise approach to managing recurrent pleural effusions.
3. Recognize the pros and cons of definitive pleural interventions for malignant pleural effusions.
4. Describe troubleshooting options for malfunctioning indwelling pleural catheters.

Scenario:

Mr. A. is a 74-year-old man, former 60-pack-year smoker (who quit ten years ago) with a past medical history of prostate cancer and GOLD stage 3B COPD. He is one of your regular patients, currently treated with tiotropium/olodaterol once daily and albuterol as needed. He presents for an urgent visit because his breathing seems worse, although his chronic non-productive cough is unchanged. He has increased his albuterol use from his usual once daily to four times daily without improvement. He describes a sensation of being “unable to take a deep breath.” He also notes an unintentional 15 lb weight loss during the past 4 months. His room air saturation is 92%, which is similar to his baseline. After a shared decision-making discussion, he elected not to pursue lung cancer screening with low-dose CT last year. His pulmonary exam is notable for decreased breath sounds bilaterally except for the left base, which has no breath sounds.

Question 1a: What is your next step for investigating Mr. A.’s change in his symptoms?

A chest radiograph is an appropriate starting point, but if a physical exam suggests the presence of a pleural effusion, bedside ultrasound is a safe, simple, and painless test easily performed in the outpatient setting. If fluid is present, consider performing a thoracentesis in the office, unless concern exists for bleeding, including patients maintained on therapeutic anticoagulation or those with known thrombocytopenia.

It is important to send appropriate body fluid studies after thoracentesis, which may include cytology, cell count and differential, and cultures, as well as corresponding serum tests (i.e. total protein and LDH). Approximately 95% malignant effusions are exudates.

Lung cancer is the most common cause (37.5%) of malignant pleural effusions (Roberts et al, 2010). In malignant effusions, the accumulation of fluid is caused by a combination of



blockage of lymphatic drainage along parietal pleural surfaces and increased inflammation. Malignant effusions can be diagnosed by pleural fluid cytology in about 60% of cases (sensitivities vary from 40% to 87%, with a mean of about 60%). A second sample increases the yield by 15%. A third sample is no longer recommended because the additional increase in diagnostic yield is meager. Diagnostic yield also depends on the type of malignancy; for example, the sensitivity of pleural fluid cytology is only 32% in effusions due to mesothelioma.

In the case of two negative pleural fluid cytology samples, it is recommended to proceed with thoracoscopy for diagnosis (parietal pleural biopsies), staging and possible treatment of suspected malignant pleural effusions. Both medical (under conscious sedation) and surgical (under general anesthesia) thoracoscopy are options (Maskell, 2003).

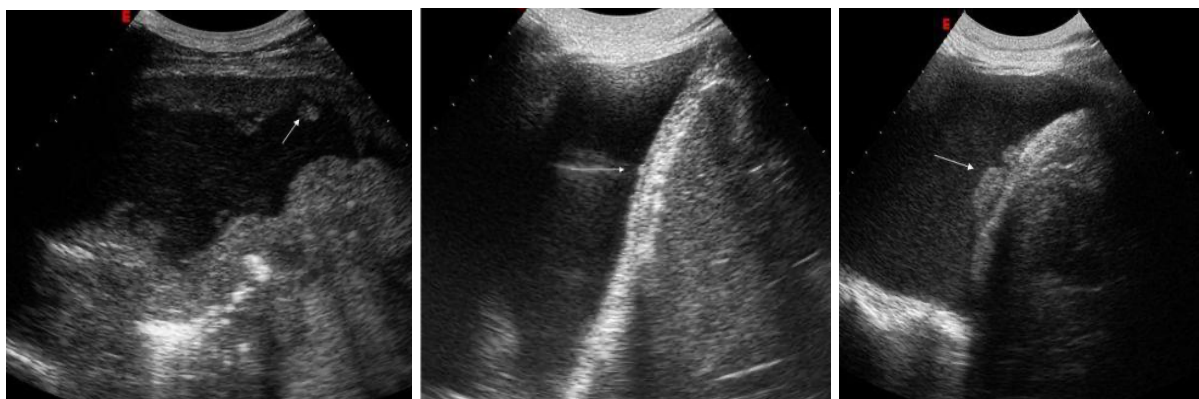
Reference	No of patients	No caused by malignancy	% diagnosed by cytology
Salyer <i>et al</i> ¹⁰	271	95	72.6
Prakash <i>et al</i> ¹²	414	162	57.6
Nance <i>et al</i> ¹¹	385	109	71.0
Hirsch ¹³	300	117	53.8
Total	1370	371	61.6

Figure above from Maskell, NA. *et al.* BTS guidelines for the investigation of a unilateral pleural effusion in adults. *Thorax* 2003; 58:ii8-17.

Question 1b: Can thoracic ultrasound differentiate Malignant Pleural Effusion from benign pleural disease?

Thoracic ultrasound correctly diagnosed malignancy in 26/33 patients (sensitivity 73%, specificity 100%, positive predictive value 100%, negative predictive value 79%), but tissue sampling remains the gold standard. Ultrasonographic features indicative of malignancy are (Quershi *et al* 2009):

- Pleural Thickening > 1 cm
- Diaphragmatic thickening > 7 mm
- Pleural nodularity



Pleural thickening >1 cm

Diaphragmatic thickening >7 mm

Pleural nodularity

If there is no improvement in symptoms with thoracentesis and there is reasonable confidence that there is cancer present in the thorax, consider the following:

- Is there endobronchial disease? Look for mediastinal shift on chest radiograph, or an endoluminal mass on chest CT; this should prompt bronchoscopy.
- Is there lymphangitic spread? In many cases, this can affect gas exchange in the pulmonary parenchyma.

Scenario continued:

Thoracic ultrasound reveals a large anechoic left pleural effusion with pleural nodularity and thickening. You decide to drain the effusion in the office.

Question 2a: Should thoracic ultrasound be used to guide thoracentesis?

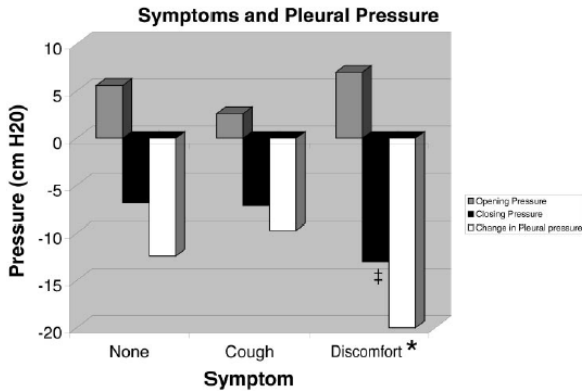
Iatrogenic pneumothorax is the most common complication of thoracentesis requiring chest tube placement and hospital admission. Historically, the pneumothorax rate after thoracentesis for pleural effusions has been reported to be 39%, although more recent data showed lower pneumothorax rates when ultrasound guidance is used. Also, ultrasound guidance for thoracentesis has reduced dry taps, hemothorax, and solid organ puncture. It is recommended to use ultrasound for any pleural intervention.

Question 2b: How much fluid should you drain? Would you use pleural manometry? When do you stop the procedure?

Classically, the thought has been to limit fluid removal to 1.5 L to avoid re-expansion pulmonary edema (RPE). However, studies have shown a low rate of RPE 0.5% with no evidence to suggest an association with the amount of fluid removed (Feller-Kopman, 2007). It is currently recommended to perform large-volume drainage to confirm symptomatic improvement after drainage. If no improvement is noted, other causes of dyspnea should be investigated (PE, pericardial effusion, pneumonia).

An elastance of less than 19 cm H₂O measured after draining 500 ml of fluid predicted a 98% chance of pleurodesis success. However, there is limited evidence defining the benefits on clinical outcomes in patients with MPE, and re-expansion pulmonary edema does occur despite the use of manometry at a rate similar to that of studies not using manometry. Use of pleural manometry is likely to vary by institution and provider.

Since we rarely perform pleural manometry during thoracenteses, we must use a surrogate for intrapleural pressure. As a general rule, it is reasonable to drain until the patient experiences vague anterior chest pain, which may signal a drop in the intrapleural pressure. A small amount of air entrained back into the pleural space may relieve the pain, and actually allow further drainage after several minutes. Although not proven, there is thought that cough is related to the lung re-expanding, and that sharp chest pain is the catheter irritating the diaphragm (sometimes felt in the shoulder as referred pain).



‡ p=0.04 from no symptom group
 * p=0.001 from cough and no symptom

Figure borrowed from Feller-Kopman, D. et al. The relationship of pleural pressure to symptom development during therapeutic thoracentesis. CHEST 2006; 129 (6): 1556-60.

The figure above illustrates that the total change in pleural pressure during thoracentesis was significantly different between the patients who developed chest discomfort and both the patients who were asymptomatic and those in whom cough developed. Discomfort was associated with the largest shift in intra-pleural pressure (white box) and this can be used as a surrogate for entrapped or trapped lung.

There is no data definitively supporting or refuting the need for post-thoracentesis chest radiographs, and thus practice will likely vary by institution and provider. Post Thoracentesis Lung Ultrasound can be a quick way to rule out post-procedure pneumothorax, especially in a patient complaining of symptoms. The presence of lung sliding reliably rules out a pneumothorax in the space being imaged.

Scenario continued:

You drain a total of 2.5 L of fluid. Mr. A. goes home and feels great! He returns the next day for chest CT which demonstrates a large left lower lobe mass and bilateral mediastinal and hilar lymphadenopathy. Pathology informs you of possible adenocarcinoma on cytology, awaiting additional stains.

Question 3: How do you determine prognosis?

In addition to TNM staging, several factors may help predict the survival of patients with malignant pleural disease, including tumor characteristics, the extent of disease, comorbidities, and performance status.

LENT score is a risk stratification system that predicts survival and selects the most appropriate pleural intervention in MPE, avoiding inpatient stay and procedure-related complications. Patients with a particularly poor prognosis may wish to minimize time spent in the hospital by choosing an indwelling pleural catheter or therapeutic pleural aspiration over attempted pleurodesis to manage their effusion.

Patients with a low-risk LENT score had a median survival of 319 days, moderate-risk LENT score had a median survival of 130 days, and high-risk LENT score, which had a median

survival of only 44 days. Obviously, the score does not replace the patient's preference or clinical judgment (Clive et al, 2014).

Survival in malignant effusions can also be predicted by the Karnofsky score (<http://www.hospicepatients.org/karnofsky.html>): KPS < 30 portends a median survival of 1.1 months; KPS > 70 is associated with a median survival of 13.2 months (Broaddus et al, 2016).

Scenario continued:

Mr. A. is diagnosed and staged by your thoracentesis. Molecular genotype testing is available from the cell block of the large sample obtained and shows no mutations. LENT score is moderate. He is seen by Medical Oncology within the next week and plans to start chemotherapy soon. About one month later, however, he returns to your clinic with 'that same feeling of not being able to take a big breath.' You confirm that his effusion has returned with ultrasound. He wonders what you can do about the fluid and whether draining it again will improve his symptoms.

Question 4: What options can you offer a patient with a recurrent malignant pleural effusion?

There are several approaches for managing a recurrent malignant pleural effusion:

- Serial thoracenteses
- Placement of an indwelling tunneled pleural catheter
- Tube thoracostomy with pleurodesis
- Medical pleuroscopy with talc poudrage
- Video-assisted thoracoscopic surgery (VATS) with talc poudrage

More than 50% of malignant effusions will reaccumulate after initial drainage, and therefore definitive pleural intervention is a priority. The primary goal in managing a malignant pleural effusion is relief of symptoms (namely dyspnea) and improvement in quality of life. This should be done via the least invasive manner while also ideally minimizing the need for repeated procedures or time in the hospital. These goals can be achieved with thoracentesis, pleurodesis, or indwelling pleural catheter (IPC). It must also be individualized, and patient preferences and other factors may influence the patient to choose over one method (Feller-Kopman et al, 2018).

Scenario continued:

Mr. A decides to undergo a second thoracentesis for now, but he asks for more information about a definitive procedure for MPE. You perform a therapeutic thoracentesis without complications and explain possible definitive treatments while waiting for post procedural CXR.

Question 5: What decision factors can you use to decide one choice over the other? What are the advantages and disadvantages of pleurodesis vs. Indwelling pleural catheter (IPC)?

Potential Decision Factors (Feller-Kopman, 2018)

Favors Pleurodesis	Favors IPC
Pleural apposition desired	Evidence of non-expandable lung
No caregiver available to help drain IPC	Desire to avoid a second procedure
History of poor compliance	Low pain threshold
Lack of insurance coverage	Tenuous respiratory status; higher risk of decompensation
Hospitalized	Preference for outpatient procedure or reluctant to get hospitalized
Low LENT score	High LENT score

Pleurodesis vs. IPC

There is no significant difference in dyspnea or Quality of Life measures (improvements sustained for 12 months) between patients who received pleurodesis vs IPC. Hospitalization length is significantly more for patients undergoing pleurodesis. Patients who underwent pleurodesis required more pleural intervention procedures subsequently vs patients who had IPC placement (22% vs 4%). IPC are associated with increased risk of infectious complications as compared to pleurodesis. Overall, risk of infectious complications with IPC remain low (Cellulitis 7.3% and pleural space infection 4.6%).

Pleurodesis Disadvantages

Pain: Patients experience chest pain following chemical pleurodesis, that resolves within one day. Chest pain is reported in 81% of those with doxycycline and relatively infrequent with talc pleurodesis (5-10%). Pleurodesis pain is controlled with the intrapleural installation of topical anesthetic like Lidocaine and PRN oral or IV pain killers (Rahman, 2015).

Respiratory decompensation: Acute respiratory distress syndrome has been reported using talc pleurodesis, especially with non-grade/ small particle talc in approximately 1%. It is theorized that the small particles are absorbed, leading to inflammation and respiratory distress; graded talc is now available with significantly lower risk.

IPC Disadvantages

Infection and malfunction: It should be noted that IPCs are associated with a comparatively higher rate of complications than pleurodesis, even though most of these complications are minor and seldom necessitate IPC removal. Complications include pleural infection, empyema, cellulitis/tunnel infection, and catheter blockage.

Pain: In less than 1% of cases, the patient may complain of persistent discomfort necessitating catheter removal.

Drainage: The patient or caregiver must perform drainage, making it difficult for patients with poor performance status or those without a suitable caregiver.

Combined Approach

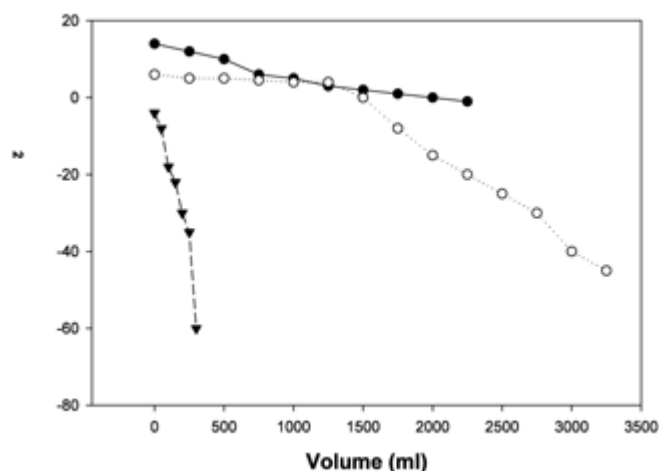
Patients with MPE and without trapped lung may be candidates for IPC placement and instilling talc through the IPC as an outpatient. The randomized IPC-Plus trial demonstrated this approach resulted in fewer catheter days, improved symptoms and better QoL (Bhatnagar, 2018). This approach has not yet been reproduced in another study, but it is promising.

Scenario continued:

You explain both approaches to Mr. A, and he understands the pros and cons of both procedures. He is ready to make his decision when you notice a pneumothorax on post-procedure CXR (after thoracentesis). Mr. A is hemodynamically stable without respiratory distress.

Question 6: What would you do next regarding the pneumothorax?

It is possible that the pneumothorax is post-procedural, but in the setting of malignancy, it is important to consider pneumothorax ex vacuo – i.e. entrapped or trapped lung – in which case, a chest tube will not enable the lung to completely re-expand.



Three pressure/volume curves are plotted. The solid circles represent a monophasic pressure/volume curve with normal pleural elastance in a case of congestive heart failure. The open circles represent a biphasic pressure/volume curve from a patient with malignant lung entrapment. The solid triangles represent a monophasic pressure/volume curve in a case of a trapped lung resulting from a remote CABG surgery. Figure from Huggins et al, 2007.

Question 7: What is the difference between trapped and entrapped lung?

	Trapped Lung	Lung Entrapment
Etiology	Remote pleural inflammation Resolved pleural infection, uremic pleuritic, hemothorax	Active pleural inflammation Active pleural infection, malignancy
Symptoms	Usually asymptomatic, chronic stable effusion	Pleurisy, dyspnea
Pressure volume curve	Monophasic linear	Biphasic
Initial pleural pressure	Negative	Can be positive
Pleural elastance	>14.5 cm H ₂ O/L of pleural fluid removed	Biphasic; initial <14.5 cm H ₂ O/L, >14.5 cm H ₂ O/L after inflection point
CXR	Absent contralateral mediastinal shift, pneumothorax ex vacuo	Contralateral mediastinal shift present
Pleural Fluid	Paucicellular transudate	Exudate
Management	Observation if asymptomatic Decortication if significant symptoms	Treat underlying process Tunneled pleural catheter, surgical decortication if persistent symptoms

Table from Huggins et al, 2018

In this case, Mr. A.'s lung did not re-expand completely, leaving the following options for managing his MPE:

- Serial thoracenteses
- Placement of an indwelling tunneled pleural catheter

Most patients find it inconvenient to return to clinic at regular intervals for repeat thoracenteses, and an entrapped or trapped lung is an indication for an indwelling pleural catheter. Dyspnea is due not only to restriction by the malignant peel, but also to physiologic changes including:

- Distension of the thoracic cavity
- Dysfunction of the affected hemidiaphragm
- Mismatch/atelectasis in the contralateral lung secondary to compression of the lung by fluid.

Sterman, et al. identified 11 patients with trapped lung physiology who had indwelling pleural catheters placed; 91% had symptom relief.

Scenario continued:

Based on CXR findings we know that Mr A's lung did not fully re-expand, leaving the option of serial thoracenteses or IPC. Mr A chooses to have an IPC placed, which is performed in the office without any issue and comments that he barely felt any pain!

The IPC (PleurX, Rocket, or Aspira catheter) is a cuffed, tunneled catheter inserted as an outpatient under conscious sedation that allows drainage at home by the patient or an attendant.

**Question 8: Does the patient need to come back to see you?**

In general, we recommend (although this may vary somewhat by practice):

- The patient should return in two weeks post-procedure for a wound check, suture removal ultrasound, and drainage (if they have not been drained that day). This gives a sense of the volume and pace of drainage, and whether they are headed towards early catheter removal.
- Patients should be also instructed to return to clinic at any time in their treatment course if their drainage is less than 50 mL for at least three consecutive drainage attempts for consideration of catheter removal.
- The patient should return in six weeks from catheter placement for repeat visit, ultrasound, and drainage (if they have not been drained that day). Further follow-up plans should be made at regular intervals following the six week appointment.

Scenario continued:

Mr. A. returns for his suture removal and does well until his next follow-up visit. At that time, he reports no drainage for the last several days, but says he didn't want to bother you about it. On ultrasound, you see a large pleural effusion without loculations. His breathing seems to be worse, but he looks stable.

Question 9: What happened and what can you do about it?

Mr. A.'s catheter is likely obstructed, commonly by fibrous clot that may contain a high number of malignant cells. Drainage can also be impacted by development of fibrinous loculations within the pleural cavity, which may occur in up to 14% of patients. In both cases of catheter blockage, this leads to fluid accumulation and breathlessness.

Flushing the catheter is the first step, but this rarely resolves the problem. There are several proposed measures for addressing an obstructed catheter:

- Administration of tPA via catheter as an outpatient is a consideration if facilities exist to facilitate this. Some have also reported combination of tPA with DNase, but overall evidence is limited. Following administration, clamp the tube for 1-2 hours before draining the fibrinolytics. If this is successful and the catheter is unobstructed, the patient can be discharged to home.
- Arrange for an elective admission for tPA with or without DNase as an inpatient, especially if loculations are present, or it appears that more than one dose of tPA will be necessary.
- If the patient is in extremis, consider a thoracentesis at a site separate from the catheter for quick relief of symptoms. Definitive treatment will still be necessary.

A multinational retrospective study of intrapleural fibrinolytic therapy for IPC-related symptomatic loculations demonstrated pleural fluid drainage increased in 93% of patients and dyspnea improved in 83% following therapy. Still, it carries a small risk of non-fatal pleural bleeding, was reported in 2 of 66 patients (Thomas, 2015; Lan, 2019).

Scenario continued:

Mr. A comes to the office complaining of fever, fatigue and chills. CBC shows leukocytosis with immature granulocytes. Patient is hemodynamically stable. You are concerned about possible intrapleural infection/empyema.

Question 10: Would you remove the IPC? Would you use TPA/DNase?

The incidence of IPC-related infection is low, with rates of cellulitis and pleural space infection of 7.3% and 4.6%, respectively. Unfortunately, there is little data regarding the management of IPC-related infection. In one case series, 72% were managed without removal of the infected IPC and mortality due to IPC infection was 9.3%. It's recommended to leave the catheter in place while connecting it to wall suction and administering antibiotics. If the infection is felt to be uncontrolled, then catheter removal is indicated. (ATS guidelines for management of malignant pleural effusion, 2018).

Coadministration of tPA and DNase through an IPC has little evidence, but it can be considered based on data from the MIST-2 trial.

Scenario continued:

Mr. A. returns to your clinic four months later. He has had diminished fluid output, less than 50 cc ml for the last three consecutive drainages. Thoracic ultrasound confirms the nonexistence of pleural effusion. You decide to remove the catheter, but during removal, IPC is fractured, and half of the catheter remains within the pleural space



Question 11: What should you do?

IPCs can fracture during removal, especially after prolonged use. Patients with retained IPC fragments do not experience additional pain or increased risk of infection based on data with over 450 days of follow-up (Fysh et al, 2012).

Clinicians should be aware that IPC removal can be problematic, but retained fragments are safe, and aggressive retrieval is unnecessary. Removal can be reserved for infection or atmospheric communication causing hydropneumothorax.

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Pre/Post-Test Questions

1. A 60-year-old male presents to your office for management of a unilateral pleural effusion. The patient had been experiencing sub-acute worsening dyspnea over the last 4-6 weeks prompting his primary care physician to order a CXR. The CXR showed a unilateral moderate effusion on the left but no other findings of note. You perform a thoracentesis in the office. Initial fluid studies are consistent with an exudate. Cytology and cultures are negative. On repeat CXR the effusion has re-accumulated. What is the next best step in management of this patient?
 - a. Referral for thoracoscopy for pleural biopsy
 - b. Placement of an indwelling pleural catheter
 - c. Repeat thoracentesis
 - d. Trial of diuresis
 - e. Watchful waiting and follow up in 3 months
2. A 65 year old male with non-small cell (adenocarcinoma) of the lung and a malignant R pleural effusion present to your office for ongoing follow up. He had his first thoracentesis 10 days ago and cytology was positive for malignancy (adenocarcinoma). He is here today to have a repeat thoracentesis and then CT scan following drainage. His prior CT scan from a year ago shows no evidence of effusion. You perform the thoracentesis without issue and remove 1.5 L of serosanguinous fluid. He denies any dyspnea post-procedure. He then has his CT scan and the radiologist calls to report a newly visualized pneumothorax. Which of the following is (are) the most likely cause(s) of the radiographic findings.
 - a. Iatrogenic post-procedure pneumothorax
 - b. Pneumothorax ex-vacuo (entrapped lung)
 - c. Pneumothorax ex-vacuo (trapped lung)
 - d. Both A and B
 - e. Both B and C
3. A 70-year-old male with non-small cell lung cancer and malignant right pleural effusion presents to discuss ongoing management of his recurrent pleural effusion. His recent CT scan shows evidence of pneumothorax ex-vacuo (entrapped lung). Which of the following is (are) appropriate management options for this patient's management of his symptomatic recurrent pleural effusion?
 - a. Medical pleuroscopy with talc poudrage
 - b. Video assisted thorascopic surgery (VATS) with talc poudrage
 - c. Tube thoracostomy with pleurodesis
 - d. Repeat thoracenteses
 - e. Placement of an indwelling tunneled pleural catheter
 - f. A, B or C
 - g. D or E