Death is the most serious outcome of tuberculosis and investigating deaths among TB patients is an essential component of TB control programs\(^1\). In order to further investigate deaths among patients with TB, the CDC has added questions in items 15 (Dead at Diagnosis\(^*\)) and 44 (Reason Therapy Stopped; If Died) of the revised Report of Verified Case of Tuberculosis (RVCT):

\[
\begin{array}{|c|c|c|}
\hline
\text{15. Status at TB Diagnosis (select one)} & \text{15. Status at TB Diagnosis (select one)} \\
\hline
\text{\ }
\hline
\end{array}
\]

\[
\begin{array}{|c|c|c|c|}
\hline
\text{Alive} & \text{Dead}\* & \text{Month} & \text{Day} & \text{Year} \\
\hline
\end{array}
\]

\[
\begin{array}{|c|c|c|}
\hline
\text{If DEAD, enter date of death:} & \text{If DEAD, was TB a cause of death? (select one)} & \text{If DIED, indicate cause of death (select one):} \\
\hline
\text{Yes} & \text{No} & \text{Unknown} \\
\hline
\end{array}
\]

CDC guidance states that \textit{Yes/Related to TB} should be selected if TB, or TB therapy, was the \textit{immediate cause} of death, an \textit{underlying cause} of death or another \textit{significant condition contributing to death}. Because determining whether TB was a cause of death is often challenging, CDPH TB Control Branch is issuing this document to help with this determination and to bring consistency among local jurisdictions reporting TB cases in California.

\textbf{How to Use this Document:}
We recommend that this tool be used by a clinician.
Steps:
1. Obtain relevant documents: a) death certificate, b) public health TB record, c) discharge summary and other relevant medical records.
2. Review documents above to evaluate extent of disease, other underlying conditions or possible causes of death, presence of life-threatening complications of TB and its treatment.
3. Proceed through appropriate algorithm on the next pages to guide answer.
4. If answer is still not clear, read through example cases for additional guidance.

This document is a framework and cannot anticipate all circumstances and cannot be a substitute for clinical judgment. Please answer \textit{unknown} only if extent of disease cannot be determined or if there is no other reasonable cause of death but extent of tuberculosis is minimal. As a point of reference, prior detailed reviews of the cause of death among a small number of persons with active TB have found that approximately 70–80% of deaths were TB related (unpublished data).

\(^*\) Definition of Dead at diagnosis: Patient died prior to being started on TB treatment \textit{and} before positive TB test results have been reported.

Last updated: May 1, 2013
Dead at Diagnosis?
Patient died prior to being started on TB treatment and before positive TB test results.

Yes → Proceed to Item 44
No

Confirm TB Case
Was diagnosis of TB confirmed by: culture, nucleic acid amplification test, pathology, or autopsy?

Yes
No

Definitely NOT TB-related Death?
1. Death resulting from an accident, homicide, or suicide or
2. Death due to a procedure (or its complications) performed for a medical condition unrelated to TB

Yes
No

Definitely TB-related Death?
1. Life threatening complications of TB (see Table 2) and no other documented cause of death or
2. Death associated with a procedure (or its complications) performed for diagnosis of TB

Yes
No

Evaluate Extent/Severity of TB (See Table 1)

Able to evaluate
No

Severe/Extensive Disease
Evidence for cause of death other than TB?

Yes
No

Moderate Disease
All cases with moderate disease require additional clinical judgment.

Yes
No

Minimal Disease
Evidence for cause of death other than TB?

Yes
No

Unable to evaluate
Request Additional Information

Still unable to evaluate

Additional Clinical Judgment Required
Determine whether TB was an underlying cause of death, contributed to death, or hastened death.
Common situations include:
A. Exacerbation of underlying condition by TB
B. Evidence of cause of death other than TB AND life-threatening consequence of TB

Generally, in cases that are not clear, TB should be considered to have contributed to or hastened death. See examples for additional guidance.

Was TB a cause of death?
Enter on RVCT

Yes
No

Unknown

Last updated: May 1, 2013
RVCT Item 44 (If Died)

Was TB a cause of death?
Enter on RVCT

Death definitely unrelated to TB?
1. Death resulting from an accident, homicide, or suicide or
2. Death due to a procedure (or its complications) performed for a medical condition unrelated to TB

No

Death definitely related to TB?
1. Life threatening complications of TB or its treatment (see Table 2) and no other documented cause of death or
2. Death associated with a procedure (or its complications) performed for treatment or diagnosis of TB or TB-related complications
3. Interaction between TB and non-TB medications likely leading to death

No

Evaluate Extent/Severity of TB (See Table 1)

Able to evaluate

Severe/Extensive Disease
Evidence for cause of death other than TB?

Yes

Related to TB disease

No

Related to TB therapy

Unable to evaluate

Request Additional Information

Able to evaluate

Moderate Disease
All cases with moderate disease require additional clinical judgment.

All

Minimal Disease
Evidence for cause of death other than TB?

Yes

Related to TB disease

No

Unrelated to TB

Unknown

Additional Clinical Judgment Required

Determine whether TB was an underlying cause of death, contributed to death, or hastened death.

Generally, in cases that are not clear, TB should be considered to have contributed to or hastened death. See examples for additional guidance.

Common situations likely include: A) Exacerbation of underlying condition by TB or TB medications; B) Evidence of cause of death other than TB AND life-threatening consequence of TB or its treatment

Choose on basis of clinical judgment

Last updated: May 1, 2013
Table 1: Extent/Severity of Tuberculosis

<table>
<thead>
<tr>
<th>Extensive disease</th>
<th>Moderate disease</th>
<th>Minimal disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary and/or Pleural TB Disease</td>
<td>All patients with pulmonary disease that do not meet the criteria of either extensive disease or minimal disease</td>
<td>All of the following:</td>
</tr>
<tr>
<td></td>
<td>▪ Miliary pattern on imaging study, or</td>
<td>▪ Sputum smear negative*</td>
</tr>
<tr>
<td></td>
<td>▪ Pathology report indicates extensive pulmonary TB disease, or</td>
<td>▪ Non-cavitary disease</td>
</tr>
<tr>
<td></td>
<td>▪ Massive tubercular empyema or pleural effusion, or</td>
<td>▪ Limited disease (e.g., single lung lesion &lt;2 cm(^2), minimal pleural effusion)</td>
</tr>
<tr>
<td></td>
<td>▪ ≥2 of the following:</td>
<td>* If sputum smear is not available, patient has minimal disease if the other criteria for minimum disease are met.</td>
</tr>
<tr>
<td></td>
<td>▪ Sputum smear positive disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ Failure to convert culture within 60 days of treatment initiation prior to death</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ Reversion of culture from negative to positive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ Cavitary disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ Bilateral disease or multi-lobar disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ Large pleural effusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ Collapse of 1 or more lobes</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Life threatening consequences of TB

<table>
<thead>
<tr>
<th>Site of Disease / Treatment</th>
<th>Life threatening consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS TB</td>
<td>▪ Meningitis</td>
</tr>
<tr>
<td></td>
<td>▪ Encephalitis</td>
</tr>
<tr>
<td></td>
<td>▪ Mass or spinal cord lesion</td>
</tr>
<tr>
<td></td>
<td>▪ Herniation</td>
</tr>
<tr>
<td></td>
<td>▪ Coma</td>
</tr>
<tr>
<td></td>
<td>▪ Other complications of CNS disease</td>
</tr>
<tr>
<td>Disseminated TB</td>
<td>bacillema</td>
</tr>
<tr>
<td>Pericardial disease</td>
<td>cardiac failure</td>
</tr>
<tr>
<td></td>
<td>myocarditis</td>
</tr>
<tr>
<td></td>
<td>cardiac tamponade</td>
</tr>
<tr>
<td>GI TB</td>
<td>bowel perforation or hemorrhage</td>
</tr>
<tr>
<td>Renal TB</td>
<td>renal failure</td>
</tr>
<tr>
<td>Hepatic TB</td>
<td>hepatic failure</td>
</tr>
<tr>
<td>Peritoneal TB</td>
<td>disseminated TB or bowel obstruction</td>
</tr>
<tr>
<td>Pulmonary/Pleural TB</td>
<td>▪ Respiratory failure</td>
</tr>
<tr>
<td></td>
<td>(Not respiratory arrest occurring at the time of death)</td>
</tr>
<tr>
<td></td>
<td>▪ Pulmonary hemorrhage with or without asphyxia</td>
</tr>
<tr>
<td></td>
<td>▪ Extensive pulmonary destruction, with or without cavitations</td>
</tr>
<tr>
<td></td>
<td>▪ Tension pneumothorax</td>
</tr>
<tr>
<td>TB Medications</td>
<td>▪ Anaphylaxis</td>
</tr>
<tr>
<td></td>
<td>▪ Hepatitis (rising INR/falling albumin + encephalopathy)</td>
</tr>
<tr>
<td></td>
<td>▪ Metabolic acidosis</td>
</tr>
<tr>
<td></td>
<td>▪ Seizure</td>
</tr>
<tr>
<td></td>
<td>▪ Severe dermatitis/Stevens-Johnson syndrome</td>
</tr>
<tr>
<td></td>
<td>▪ Thrombocytopenia/Leukopenia</td>
</tr>
</tbody>
</table>

Table 3: Pathologic / Autopsy findings consistent with TB

<table>
<thead>
<tr>
<th>Pathologic Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Caseating granulomas</td>
</tr>
<tr>
<td>▪ Non-caseating granulomas</td>
</tr>
<tr>
<td>▪ Granulomatous inflammation</td>
</tr>
<tr>
<td>▪ Caseous necrosis</td>
</tr>
</tbody>
</table>
Examples:

YES/RELATED TO TB DISEASE/Therapy:

55 yo man with smear positive pulmonary TB and end stage liver disease dies in the hospital. He started TB medications (RIPE) four weeks prior to death. He was hospitalized three weeks later with hepatic encephalopathy and shortness of breath. Transaminases were elevated upon admission. CXR prior to death showed diffuse infiltrates or edema. No autopsy is performed. TB is not listed on his death certificate.

The timing of this patient’s liver disease exacerbation is likely the result of TB medication side effects. As such, Related to TB Therapy should be chosen on item 44 of the RVCT. If this same patient had died of a massive variceal bleed without acute exacerbation of liver disease, then Unrelated to TB should be chosen.

67 yo man with baseline severe but stable CAD (planned for CABG) presents to his PMD with fevers, weight loss, and pleuritic chest pain. He is diagnosed with cavitary, smear-positive TB and starts on therapy. Over the next few days he becomes increasingly short of breath. He is found dead at home. Autopsy confirms cavitary TB and severe CAD (85% occlusion of the LAD) but no acute thrombus.

One reasonable explanation in this case is that in the setting of reduced cardiac perfusion, the increased work of breathing and stress from the tuberculosis resulted in ischemia induced arrhythmia. In this case TB likely contributed to death and Related to TB Disease should be chosen on item 44.

73 yo woman is admitted to the hospital with shortness of breath and found to have a large right sided pleural effusion with surrounding infiltrate. She is intubated and a chest tube is placed. Sputum culture is positive for Staphylococcus aureus and she is started on appropriate therapy for bacterial pneumonia. She also is found to have hematuria and a right lower extremity DVT. Two days later she becomes difficult to ventilate. CXR shows a tension pneumothorax on the left. Soon thereafter a code blue is called and she is not able to be resuscitated. Several weeks after death, 2 of 3 pleural fluid samples become culture positive for Mtb. Stenotrophomonas maltophilia also grew from 1 of 3 pleural fluid samples. No sputum was sent for AFB smear or culture.

This case should be classified as extensive disease even though no sputum was obtained (large effusion, bilateral disease). Although she had cultures that were positive for other bacteria, the fact that she had multiple pleural fluid specimens positive for Mtb and that she had life-threatening complications of TB (tension pneumothorax) make it unlikely that her disease was exclusively caused by staph or stenotrophomonas. TB very likely contributed to her death and Yes should be chosen on item 15.

33 yo woman with AIDS (CD4 count = 23) not on ARVs is admitted to the hospital with fevers, weight loss, and subacute headache. Cryptococcal meningitis is diagnosed on the basis of positive CSF cryptococcal antigen and treatment is initiated. However, her disease is slow to respond to therapy and 10 days after admission she suffers from cerebral herniation and dies. Subsequently, AFB culture of the CSF returns positive for Mtb. TB is not listed as a cause of death on the death certificate.

Although it is difficult to disentangle the effect of the cryptococcal infection from the tuberculosis, it seems likely that concomitant CNS TB played at least a contributing role in her death. Yes should be chosen on item 15.

NO/UNRELATED TO TB:

62 yo woman with DM is diagnosed with TB cervical lymphadenitis by FNA and culture. She begins on RIPE and does well. Two months following treatment initiation, she develops a fever and a cough. She is admitted to the hospital with a diagnosis of pneumonia. She worsens in the hospital and is intubated with ARDS and requires vasopressor therapy. Sputum and blood cultures grow MRSA. After 4 days without improvement, her family and medical team change her goals of care to comfort and she dies. No autopsy is performed.

There is a clear other cause of death and her TB disease should be classified as minimally severe extrapulmonary TB. Unrelated to TB disease should be chosen on item 44.

83 yo man previously healthy except for osteoarthritis and hypertension treated with a diuretic is diagnosed with smear positive TB during workup for a large pleural effusion. He starts on RIPE. Two weeks later, he is found dead at home. Autopsy reveals a large hemorrhagic stroke.

Last updated: May 1, 2013
Although this is extensive pulmonary disease, the stroke is a cause of death that was not likely to have been hastened or contributed to by TB or TB treatment. Choose Unrelated to TB disease on item 44.

55 yo woman with poorly controlled diabetes is diagnosed with smear positive TB. CXR shows minimal lingular infiltrate. She is started on RIPE. She subsequently converts her smear and culture to negative. Her diabetes continues to be poorly controlled and she requires amputation of 4 toes. During her hospitalization, she develops MRSA pneumonia requiring intubation and vasopressors. She continues to deteriorate and she is made DNR/DNI. She dies in the ICU 2 days later.

This is moderate TB that responded to treatment. TB was not likely to have contributed to or hastened her death since that stemmed from complications of her diabetes. Choose Unrelated to TB disease on item 44.

UNKNOWN:
47 yo man with no significant past medical history is diagnosed with asymptomatic smear negative, culture positive pulmonary TB as part of a contact investigation. CXR findings are 2 small nodules in the left apex. He is treated for TB with RIPE. His 1 month evaluation had negative cultures and his CXR is slightly improved. He is found dead at home. Autopsy findings do not reveal another cause of death. TB is listed as a cause of death on the death certificate.

With minimal disease apparently responding to therapy, TB seems unlikely to have caused death, but in the absence of another cause in this otherwise healthy person, TB cannot be ruled out as a cause of death either. In this situation, the role of TB can be deemed to be unknown (despite the fact that TB was listed as a cause of death on the death certificate). Unknown should be chosen on item 44.

Reference List