Review Article

Management of chronic pleural tuberculosis and non-tuberculous empyema in the 21st century

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Abstract: This review addresses complexities in managing pleural tuberculosis (TB) and non-TB empyema. Historically, TB, often termed "the mother of thoracic surgery", has witnessed a dramatic transformation from invasive surgical interventions to the dominance of medical therapy with the advent of effective anti-TB agents in the mid-20th century. This shift marked a pivotal moment in the treatment landscape, with medical therapy taking precedence and surgical methods reserved for diagnostic purposes or complications. In contrast, the history of non-TB empyema, dating back to Aristotle, evolved from open drainage and open surgery to minimally invasive surgery and fibrinolytic therapy. The review delves into the nuances of these conditions, exploring their clinical manifestations and the state-of-the-art management strategies that have emerged over time. Advancements in imaging modalities, such as computed tomography (CT), complemented by diagnostic laboratory techniques like the GeneXpert MTB/RIF assay, have revolutionized the diagnosis of TB, enhancing accuracy and expediting the process. The review also highlights the distinct clinical presentations of pleural TB and non-TB empyema, underscoring the challenges and intricacies in their management. It thoroughly explores the historical evolution, current diagnostic approaches, and advanced management strategies for these conditions, offering valuable insights for the learner.

Keywords: Empyema; pleural tuberculosis (pleural TB); pleural empyema

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Introduction

Pleural tuberculosis (TB) and non-TB empyema are distinct pathologies, each presenting unique challenges to healthcare providers. To fully grasp the complexities of these conditions, it is essential to explore their pathogenesis and pathophysiology.

The pathogenesis of pleural TB often begins with the reactivation of latent *Mycobacterium tuberculosis* infection (1). The bacteria spread from the lung parenchyma to the pleural space, eliciting an immune response that accumulates fluid and inflammatory cells in the pleura. This process is characterized by a delayed hypersensitivity

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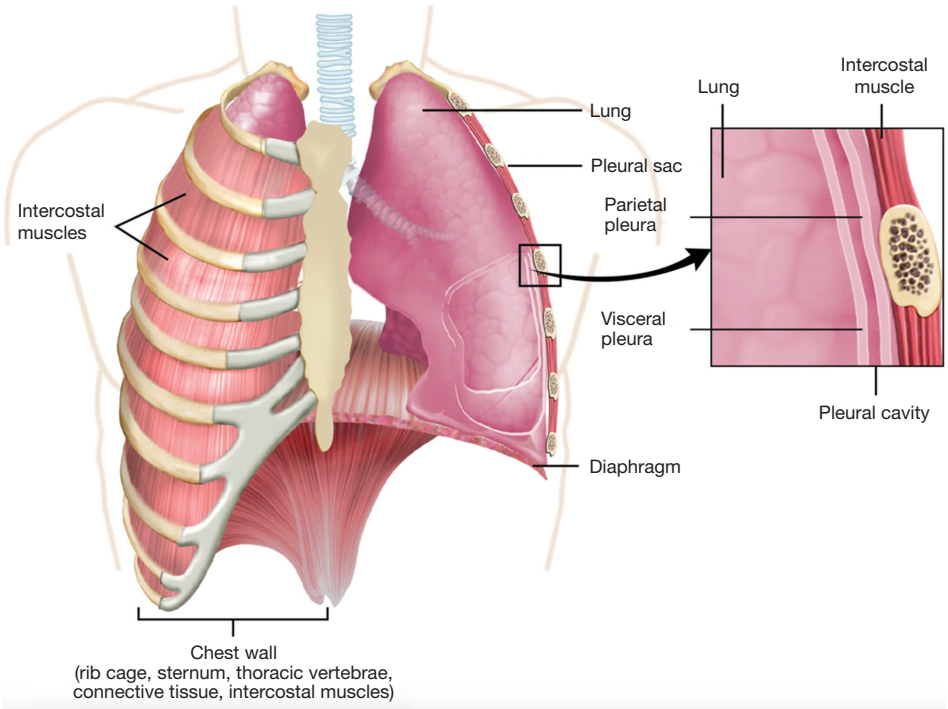

Figure 1 Anatomy of the pleural space. Illustration from Anatomy & Physiology, Connexions Web site. Available online: http://cnx.org/content/col11496/1.6/, Jun 19, 2013. Creative Commons Attribution 4.0 International License.

reaction central to pleural effusion formation.

In contrast, non-TB empyema typically results from bacterial infections, such as pneumonia, that extend into the pleural space. The accumulation of pus in the pleural cavity is a response to this infection, leading to a more acute inflammatory reaction compared to pleural TB.

The global prevalence of pleural TB remains obscure. Still, estimates suggest that pleural TB accounts for approximately 5% of all TB cases in endemic areas (2), and therefore the second cause of extra-pulmonary TB (3). As a highly geographically distinct disease, the prevalence of the pleural form may be higher in disease-dense regions (4).

Special populations include people co-infected with the human immunodeficiency virus (HIV), who demonstrate increased susceptibility to TB manifestations, including the pleural form (5).

Other susceptible populations have migrant and refugee populations, often encountering considerable barriers to effective healthcare (6), potentially resulting in complications and augmented disease transmission (7).

As expected in most diseases, socioeconomic factors significantly impact treatment outcomes (8). Additionally, pleural TB has economic and sociocultural consequences (9), often impeding an individual's capacity to work for an extended period and precipitating social ostracism due to disease-associated stigma (10).

Similar to TB, non-TB pleural empyema represents a significant public health problem (11,12), with a vast number of disparities that are influenced by factors including average life expectancy, pneumonia prevalence, accessibility to anti-pneumococcal vaccines, antibiotic resistance trends, availability of advanced treatments such as fibrinolytic, and prompt access to optimal medical and surgical care (13-16).

To facilitate understanding, we provide a detailed figure of pleural anatomy (*Figure 1*). This visual aid illustrates the thoracic structures involved in pleural diseases, serving as a reference point throughout this review.

History of pleural TB

Historically dominated by surgical interventions, TB has been considered by many "the mother of thoracic surgery" (17). From highly invasive thoracoplasties (18), the management of the disease transformed with the advent of anti-TB agents like streptomycin by the mid-20th

Table 1 Comparative summary between pleural TB and non-TB empyema

Criteria	Pleural TB	Non-TB empyema
Clinical presentation	Insidious onset, fever, night sweats, pleuritic chest pain	Acute onset, high fever, chest pain, dyspnea
Laboratory findings	Lymphocytic pleural effusion, elevated ADA levels	Neutrophilic pleural effusion, low pH and glucose levels
Imaging features	Pleural thickening and pleural effusion on ultrasound or CT scan	Loculated effusion on chest X-ray, or ultrasound, thickened pleura on, loculations, dense fluid or split pleura on CT scan
Microbiological tests	Positive *Mycobacterium tuberculosis* culture or PCR	Positive bacterial culture, often gram-positive cocci

TB, tuberculosis; ADA, adenosine deaminase; CT, computed tomography; PCR, polymerase chain reaction.

century (19), shifting swiftly from surgical modalities.

The evolution of anti-TB agents [e.g., isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB)] (20) advanced medical therapy as the primary treatment modality, reserving surgical interventions for cases presenting with complications like bronchopleural fistulas (21) or drug-resistant forms (22).

Now, in the early 21st century, the diagnosis of TB has been enhanced by advanced imaging modalities [e.g., computed tomography (CT) and magnetic resonance imaging (MRI)] (23) complemented by enhanced laboratory techniques (e.g., GeneXpert MTB/RIF assay), expediting an accurate diagnostic process (24-26).

History of non-TB empyema

Although the history of pleural empyema is said to be traced back to Aristotle 2,000 years ago (27), the first clinical reports of the disease date back to the 1800s by surgeons such as Bell, Playfair, Meyer, and Bulau (28).

Primarily managed with open drainage (29,30) or surgeries such as rib trephining (31), the introduction of tube thoracostomy as a minimally invasive alternative only became standard during World War II (32).

In the mid-20th century, the antibiotic revolution, spearheaded by agents like penicillin (33), substantially influenced empyema management by addressing its bacterial cause. Subsequently, decortication through thoracotomy emerged as a surgical mainstay for organized empyema cases (34).

A main technological advancement in the 21st century was the introduction of video-assisted thoracoscopic surgery (VATS), which offered similar results for the early stages of the disease, with reduced pain and gained better acceptance (30). Fibrinolytic agents [e.g., streptokinase, urokinase, deoxyribonuclease (DNase), and alteplase] also gained popularity, aiding drainage and empyema resolution without operations (35).

Clinical presentation and diagnosis

Understanding the clinical presentation and accurately diagnosing pleural TB and non-TB empyema are critical for effective management.

A comparative summary of both diseases has been provided in *Table 1*.

Pleural TB primarily manifests as a chronic pleural effusion, often accompanied by an array of systemic symptoms: persistent cough, nocturnal hyperhidrosis, significant weight loss, and intermittent fever (36).

Direct isolation of *Mycobacterium tuberculosis* remains arduous due to prolonged cultivation periods and a diagnostic yield of only 63% (37).

Alternative diagnostic modalities encompass pleural fluid analysis of adenosine deaminase (ADA) levels with (cutoff >40 U/L) (38), which has sensitivity of 92% and a specificity of 90% and/or molecular-based detection via the GeneXpert MTB/RIF assay, which has a sensitivity of 98% and specificity of 98% (39) in TB empyema and 40–50% in conventional pleural TB (39). This reduced yield can be explained by the pleural effusions being mostly a hypersensitivity reaction.

Unlike pleural TB, non-TB empyema predominantly presents acutely and is characterized by fever, pleuritic chest pain, dyspnea, and a productive cough (40).

Etiologically, non-TB empyema is an infectious pleural effusion engendered not by *Mycobacterium tuberculosis*, but by a plethora of pathogens.

Classic bacterial causes are *Streptococcus pneumoniae*, *Staphylococcus aureus*, and various *Gram-negative bacilli* (41) and anaerobes such as *Fusobacterium nucleatum* and/or *Streptococcus spp.* (42).

Table 2 Key distinguishing features of pleural TB and non-TB empyema

Features	Pleural TB	Non-TB empyema
Onset	Gradual	Rapid
Symptoms	Mild fever, weight loss, chest pain	High fever, severe chest pain, dyspnea
Pleural fluid characteristics	Lymphocytic, high ADA	Neutrophilic, low pH, high LDH
Radiological signs	Unilateral effusion, pleural thickening	Loculated effusions, possible lung consolidation
Causative agent	*Mycobacterium tuberculosis*	Various bacteria, often community-acquired

TB, tuberculosis; ADA, adenosine deaminase; LDH, lactate dehydrogenase.

Depending on the hospital and geographic country, specific causes vary based on local microbiology. Culture sensitivity also varies locally but typically ranges at around 46% for pleural fluid, 46.9% for tissue culture, and 62.7% for a combination of tissue and culture (43). Some more optimistic reports have described a yield of up to 92% (44).

Although the most common cause is pneumonia, there are other etiologies such as esophageal perforation, thoracic surgical interventions, or cervical infections (45).

Diagnostic criteria for non-TB empyema necessitate pleural fluid analysis showing pus, a positive fluid culture or gram stain, lactate dehydrogenase (LDH) levels surpassing 1,000 U/L, or a pH, typically below 7.2 (46).

To further clarify, In *Table 2*, we provide a summary of key distinguishing features between the two diseases.

We provide distinct clinical vignettes about these two diseases.

Case presentation 1

Mr. A, a 45-year-old male, presented with a 3-week history of low-grade fever, night sweats, and left-sided chest pain. He had a history of exposure to TB. He had decreased breath sounds over the left lower lung field on examination. Chest X-ray revealed left-sided pleural effusion. Pleural fluid analysis showed lymphocytic predominance and elevated ADA levels. A diagnosis of pleural TB was made based on these findings.

Learning point

This vignette illustrates the typical presentation and diagnostic approach for pleural TB, emphasizing the importance of history, physical examination, and targeted investigations.

Case presentation 2

Mrs. B, a 60-year-old female with a history of chronic obstructive pulmonary disease (COPD), presented to the emergency department with a 5-day history of high fever, sharp right-sided chest pain, and shortness of breath. She had a productive cough with greenish sputum. Her recent medical history included a severe bacterial pneumonia 10 days prior. On physical examination, she exhibited respiratory distress and decreased breath sounds over the right lower lung field. A chest X-ray revealed a right-sided loculated pleural effusion.

Pleural fluid analysis showed a neutrophilic predominance, low pH, and elevated LDH levels. Gram stain of the pleural fluid revealed gram-positive cocci. Based on these findings, a diagnosis of non-TB empyema was made.

Learning point

This vignette highlights the acute presentation and diagnostic criteria for non-TB empyema, underscoring the importance of considering past medical history, especially recent bacterial infections, in the diagnostic process. The case also emphasizes the role of pleural fluid analysis and imaging in confirming the diagnosis.

Management strategies

Managing pleural TB and non-TB empyema includes various therapeutic tools, requiring a balance of evidence-based practices and practical considerations.

A treatment algorithm (*Figure 2*) outlines main steps from diagnosis to treatment completion, including first-line therapies, and surgical interventions.

The standard of care for pleural TB typically involves a 6–9-month course of anti-TB therapy, adhering to WHO guidelines. For non-TB empyema, the approach is antibiotic therapy tailored to culture results and drainage procedures, following American Thoracic Society (ATS)/ Infectious Diseases Society of America (IDSA) guidelines.

This section will explain the broader spectrum of available therapies, providing clarity on conventional

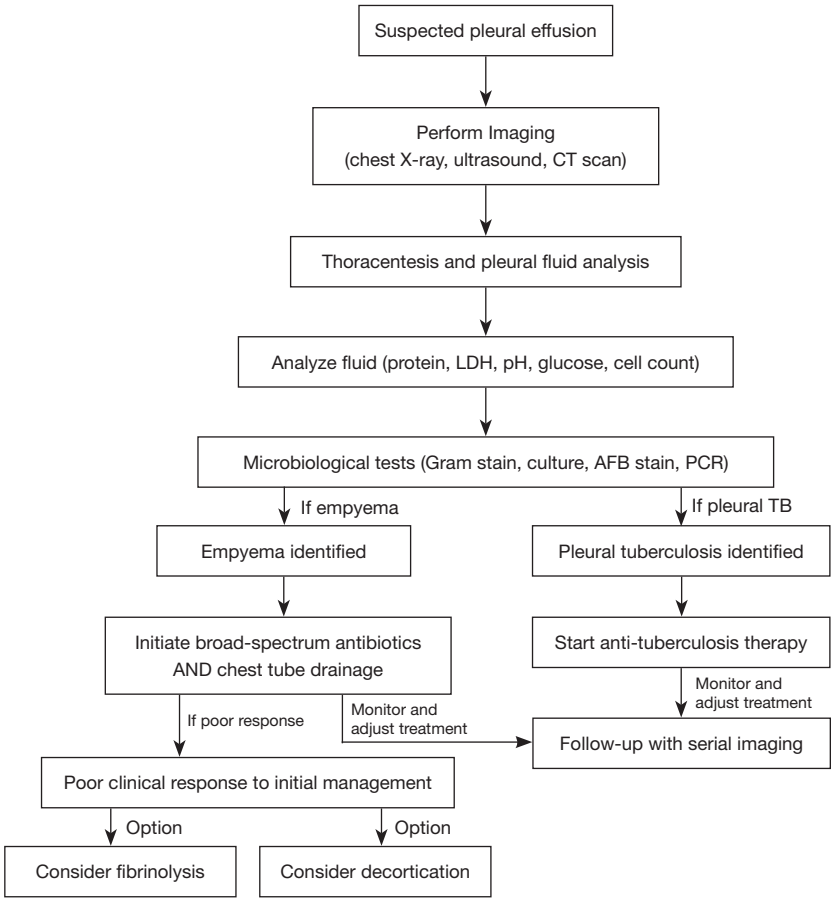

Figure 2 Algorithm for management of pleural effusion. CT, computed tomography; LDH, lactate dehydrogenase; AFB, acid-fast bacilli; PCR, polymerase chain reaction; TB, tuberculosis.

practices and their rationale.

(I) Medical management of pleural TB

The cornerstone of pleural TB management is anchored in a combination regimen comprising INH, RIF, PZA, and EMB (47).

This therapeutic strategy is bifurcated into an initiation phase, where INH, RIF, PZA, and EMB are administered daily over 2 months, followed by a continuation phase of daily INH and RIF over 4 months (47).

Special considerations may necessitate extending the consolidation phase to 7 months, such as extensive TB cases (high burden of disease), hepatotoxicity, or concurrent HIV infection (47). Cases that require a change in the treatment regimen require an extension of the consolidation phase to at least 9 months.

Adjunctive interventions, such as prednisolone, may be contemplated in cases with pronounced pleural thickening or dyspnea (48). However, the evidence underscoring its efficacy remains low (49).

Periodic evaluations, sputum cultures, liver function tests, and serial chest radiographs are imperative to check therapeutic progress and identify potential adverse reactions (50). Antibiotic resistance is a significant public health problem, particularly in developing countries. Therefore, for all patients initiating treatment and in special situations where drug-resistant TB is suspected, drug susceptibility testing is mandatory (51).

HIV patients are required to begin simultaneous antiretroviral therapy (ART) once stable. TB treatment must always precede the ART treatment.

(II) Medical management of non-TB empyema

Pleural empyema's medical management consists of broad-spectrum antibiotics, including anaerobic coverage (52). Antibiotic regimens can then be adjusted based on pleural fluid cultures and sensitivities and typically last 14 to 21 days (53). Conventionally, intravenous antibiotic is started and then transitioned or changed to oral formulations contingent on clinical improvement and microbial sensitivity profiles.

(III) Indications for chest tube placement

Therapeutic drainage of large effusions in both CPT and non-TB empyema is usually indicated.

Thoracentesis may allow diagnosis (54), allowing for fluid cultures, biochemical assessment, and cytologic analyses. Additionally, clinically, patients may experience pulmonary expansion, symptom improvement, and functional enhancement. Installation of a chest tube or small pigtail may be a better initial choice for continuous drainage, especially considering ultrasound-guided insertion (55). Optimal drainage can also potentiate the penetration of anti-TB medications into the pleural space (51).

Management involving chest tube placement, once pleural TB has been initially drained, remains a topic of debate, as such effusions might remit following concomitant antibiotic therapy (56).

While tube thoracostomy inherently bears risks—spanning infection, iatrogenic injury, and pain (57)—recent incorporation of small-bore chest tubes (58) and auxiliary imaging for placement have mitigated these risks, enhancing precision (59). Contemporary high-level evidence supports the safety and efficacy of smaller drains, dispelling some entrenched surgical myths (60).

Permanent chest tube placement can be a source of significant discomfort, making routine long-term placement generally inadvisable, except for chronic empyema's in patients who are not surgical candidates and have not achieved source control with fibrinolytic therapy (61).

(IV) Fibrinolytics

Intrapleural use of fibrinolytics in non-TB empyema has traditionally been indicated in patients who are not good candidates for surgical treatment due to comorbidities or frailty (62). However, additional indications such as residual infections after decortication or even as a primary treatment instead of VATS surgery may be considered depending on the provider's choice (63). Fibrinolytic superiority to surgery in adults has yet to be proven (64-66). Cost-effectiveness between the two techniques may be similar (67), with length of admission being shorter in surgical patients (66).

Several intrapleural medications have been historically used, such as streptokinase (68,69), urokinase (63), DNase (70), alteplase (71), and their combination (72). The MIST-2 trial favors a combination of DNase and alteplase as the most effective treatment strategy (72). Despite the evidence, it is still expected to have a high amount of heterogeneity regarding treatment choice (73), dosages (74), and frequency of administration (75).

Regarding the role of pleural TB, fibrinolytic therapy has no universally accepted indication (76,77), with the exception being pleural effusions with a high number of differential diagnoses or a concurrent non-TB empyema (35).

(V) Surgical and interventional management of pleural disorders

Pleural biopsy

Indications for pleural biopsy emerge when malignancies or TB constitute potential differential diagnoses. Tissue analysis allows for a high diagnostic accuracy (78) and may be done through needle biopsy (79), medical thoracoscopy (80,81), or VATS. If needed, VATS can be performed awake (82), and the procedure is associated with a prompt postoperative recovery and a high diagnostic yield (83). In non-TB empyema's, pleural peel is sent to pathological analysis when the differential diagnosis is high for pleural malignancies.

Decortication

Decortication entails a surgical exploration of the thoracic cavity, coupled with the aspiration of pleural effusion and the surgical excision of fibrinous and inflammatory deposits from the visceral pleura to promote pulmonary re-expansion, clean the chest cavity and reduce bacterial load (84).

This surgical intervention is predominantly executed through minimally invasive methodologies, notably VATS (85). Robotic-assisted thoracic surgery (RATS) has also been utilized (86), yet there is no evidence to support it over the VATS technique.

VATS allows faster recovery, reduced pain, and reduced respiratory complications compared to thoracotomy (87). Still, the surgery does have well-described complications (88) such as bleeding needing a transfusion, air-leak, respiratory failure, postoperative myocardial infarction, acute kidney

injury, mechanical ventilation, among others (89).

As for pleural TB, decortication was a widely used technique of mostly historic interest (90). It is currently only routinely performed if patients present with chronic pleural thickening despite aggressive and prolonged medical treatment (91).

Extrapleural pneumonectomy (EPP)

EPP was first described for treating pleural TB refractory to thoracoplasty (92). With the advances in medical treatment, this technique has fortunately been essentially extinct for this indication (93).

EPP has no role in the management of non-TB empyema's.

Pleurodesis

There is no robust evidence advocating chemical pleurodesis to prevent the recurrence of pleural TB. Additionally, this intervention might render subsequent surgical access to the thoracic cavity more troublesome and may prove ineffective due to trapped lung (94).

Regarding non-TB empyema, chemical pleurodesis is a contraindication due to the potential augmentation of complications and suboptimal infection management (95).

(VI) Management of complications

In addressing the spectrum of empyema, it is crucial to highlight the challenging scenario of empyema with bronchopleural fistula. This condition, often overlooked, represents a clinical challenge, frequently arising from complex etiologies such as pulmonary mycosis, TB or non-TB mycobacterial infections, complications following pulmonary resection, or pulmonary abscesses.

Empyema with bronchopleural fistula is characterized by its refractory nature and the complexity of treatment, requiring antimicrobial therapy, and bronchoscopy and/or surgical treatment, which escapes the scope of this review.

(VII) Integration of treatment alternatives

In integrating treatment alternatives for non-TB empyema and pleural TB, it is imperative to consider the levels of evidence supporting each intervention and the data on cost-effectiveness to guide clinical decisions.

For non-TB empyema, the administration of broad-spectrum antibiotics, including anaerobic coverage, is strongly supported by high-quality evidence (Level I) (52), with the regimen's adjustment based on culture sensitivities. The transition from intravenous to oral antibiotics is supported by evidence (Level II) (52) that reflects clinical improvement and microbial sensitivity profiles.

Chest tube placement, a key component of empyema management, is backed by substantial evidence (Level I) (52) for its indication in draining large effusions and, in the case of TB, facilitating the delivery of anti-TB medications into the pleural space. Using smaller-bore chest tubes and image-guided placement has decreased morbidity (Level II evidence) (55,60), enhancing patient comfort and reducing procedure-related risks.

Fibrinolytic therapy in non-TB empyema offers an alternative to surgical intervention, particularly for patients with significant comorbidities (Level II evidence) (65). While the cost-effectiveness of fibrinolytic compared to surgery is similar (Level III evidence) (67), the length of hospital stay tends to be shorter for patients undergoing surgery (Level II evidence) (67). Specific agents like DNase and alteplase are supported by trials such as MIST-2 (Level I evidence) (72).

Surgical management for empyema includes VATS and decortication, supported by high-level evidence (Level I and II) (88) for their efficacy in rapid recovery. Despite known complications, VATS is favored over open thoracotomy for its lower incidence of respiratory complications and postoperative pain (Level II evidence) (30).

The role of pleural TB management in surgery, particularly decortication, is reserved for cases of chronic pleural thickening after prolonged medical therapy, as suggested by lower-level evidence (Level III) (17). EPP, once a treatment for pleural TB, has become obsolete due to medical advancements (Level IV evidence) (92).

Chemical pleurodesis is not commonly advocated in pleural TB or non-TB empyema due to a lack of solid evidence and potential complications that can arise from the procedure (95).

Integrating these treatment alternatives must be supported by thoroughly understanding the evidence and cost-effectiveness. This ensures that each patient receives the most appropriate, evidence-based care tailored to their clinical context and the physician's place of practice. This approach promotes medically and economically optimal outcomes, aligning healthcare interventions.

Discussion

This review, while comprehensive, has its limitations. The

rapidly evolving nature of healthcare, especially in the context of the COVID-19 pandemic, means that some recent developments may be excluded. Additionally, the variability in healthcare access and quality worldwide may affect the generalizability of our work.

Both TB effusions and non-TB pleural empyema currently pose challenges for medical professionals. As advancements have been made in healthcare, these conditions have become less common in developed countries.

Increased migration and social conflicts may have created a surge in these diseases in populations living in vulnerable conditions without data to analyze their impact.

There remain significant knowledge gaps and controversies in the diagnosis and treatment of pleural TB and non-TB empyema. For instance, the optimal use of surgical interventions in pleural TB and the management of drug-resistant forms of non-TB empyema are areas of ongoing debate. These gaps highlight the need for further research, particularly in understanding the benefits of different therapeutic approaches.

Conclusions

In conclusion, this review thoroughly explores TB and non-TB pleural empyema, highlighting their historical context, clinical presentations, and current management strategies.

Key takeaway points

- A high index of suspicion is crucial for the timely diagnosis of pleural TB, and medical treatment is the cornerstone of management.
- Managing non-TB empyema requires a multidisciplinary approach tailored to the patient's needs, including antibiotics, drainage, and potentially surgery or fibrinolytics.

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Footnote

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