# The Great Masquerader: Tuberculosis Presenting as Community-Acquired Pneumonia

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## Abstract

According to World Health Organization estimates, tuberculosis (TB) and lower respiratory tract infections (LRTIs) are both among the top 10 global causes of death. TB and community-acquired pneumonia (CAP), if mortality estimates are combined, would rank as the third most common cause of death globally. It is estimated that each year there are approximately 10 million new cases of TB that are associated with approximately 1.2 million deaths, and almost 450 million new episodes of LRTI (synonymous with CAP) with approximately 4 million associated deaths. Globally, *Streptococcus pneumoniae* remains the most common cause of CAP. However, although well documented, it is not widely appreciated that in several parts of the world, including sub-Saharan Africa, Asia, and South America, *Mycobacterium tuberculosis* is an important cause of CAP, if not the most common organism isolated in such settings. Thus, CAP due to *M. tuberculosis* is not uncommon in some parts of the world with up to a third of cases being attributable to *M. tuberculosis*. Consequently, TB remains an important clinical entity in the intensive care unit in these settings. Despite its frequency and importance, there are very limited data about TB CAP. In this review we discussed the epidemiology, immunopathogenesis, clinical presentation, diagnosis, management, prognosis, and prevention of TB CAP. The utility of newer diagnostic approaches is highlighted.

**Keywords**
- tuberculosis
- community-acquired pneumonia
- lower respiratory tract infection
- intensive care unit
- critically ill

Lower respiratory tract infections (LRTIs), including community-acquired pneumonia (CAP) and tuberculosis (TB), are listed among the World Health Organization's (WHO's) top 10 global causes of death.[1] TB is arguably one of the biggest killers of mankind with almost a billion people succumbing to the disease in the last two centuries. LRTI, synonymous with CAP, remains the most deadly communicable disease, which caused almost 3 million deaths globally in 2016.[1] In 2018 there were an estimated 10 million new TB cases and approximately 1.2 million deaths due to TB.[2] Although both TB and CAP are infections of the lower respiratory tract, they are often thought of as separate entities as TB is classically a more indolent disease presenting over weeks to months and, often, is not associated with acute respiratory compromise. By contrast, CAP is generally associated with a short history of several days, is rapidly progressive, and is more often associated with respiratory compromise. However, although there is good evidence to the contrary, it is widely believed that *Mycobacterium tuberculosis* is not an important cause of CAP, which is an acute disease. In reality, in TB-endemic countries, and particularly in TB and

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human immunodeficiency virus (HIV)-endemic settings, TB-associated CAP (TB CAP) is not uncommon.[3] Indeed, in several parts of the world, *M. tuberculosis* is the most common pathogen isolated in those with presumed CAP. Despite the importance of this entity, to our knowledge, there have been no detailed reviews on TB CAP. This article provides a comprehensive overview of TB CAP and discusses the epidemiology, clinical presentation, immunopathogenesis, diagnosis, and clinical management of TB CAP. Other aspects such as posttuberculous lung disease and preventing TB CAP are also addressed.

## Epidemiology

Although the incidence of TB has been slowly declining over several years, it is far from eradicated, and TB remains among the top 10 killers globally.[1,4] Although TB continues to occur in almost every part of the world, the eight highest burden countries (India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa) represent almost two-thirds of the total disease burden. The 22 high-burden TB countries include Angola, Bangladesh, Brazil, China, DPR Korea, DR Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Pakistan, Philippines, Russian Federation, South Africa, Thailand, Tanzania, Viet Nam, Cambodia, and the Central African Republic.[2] There are also many intermediate-burden countries, which include those in South East Asia and South America, where TB is still rife. There are several cross-cutting themes that modulate the presentation, diagnosis, and management of TB and TB CAP, including HIV co-infection, drug-resistant TB (DR-TB), and TB in children. Indeed, HIV-infected persons are exquisitely susceptible to TB with an over 100-fold increased risk of TB infection compared with HIV-uninfected persons. Globally, there are almost 500,000 new cases of multidrug-resistant (MDR)-TB or extensively drug-resistant (XDR)-TB annually and approximately 25% of all *M. tuberculosis* isolates are resistant to at least one major anti-TB drug. Approximately 11% of the TB burden is in children and TB CAP remains an important entity in this vulnerable subpopulation. Clinical presentation in HIV-infected patients[5] is atypical and lack of cavitary disease, and lower lung zone infiltrates, consolidation, pleural effusion, and lymphadenopathy are more common. TB control in several parts of the world is being subverted by the resurgence of MDR-TB; resistance to rifampicin and isoniazid, the two frontline antituberculous drugs. EDR-TB (additional resistance to fluoroquinolones and aminoglycosides) has also increased globally. Despite the use of newer second-line drugs such as bedaquiline and linezolid, approximately 25% of patients with MDR-TB and approximately 35% with XDR-TB[6,7] still have poor outcomes. In countries like South Africa, the total burden of DR-TB is approximately 5% and therefore susceptibility testing is routinely performed in all isolates. About 15% of the burden of TB is in children who often present with atypical radiological features and confirming the disease microbiologically in this subgroup is challenging.[8,9] These three cross-cutting themes have relevance to the epidemiology, diagnosis, and management of TB CAP.

### How Common Is TB CAP?

►**Table 1** outlines the frequency of TB CAP in those presenting with acute LRTI. Collectively, the frequency of TB CAP varied from 1% in Beijing, China[10] to almost 61% in Cote d'Ivoire.[11] Overall, there seemed to be a higher prevalence of TB CAP in those presenting with acute LRTI in HIV-endemic countries. For example, in a large study conducted in Pietermaritzburg in the KwaZulu-Natal Province of South Africa (the study HIV prevalence rate was 69%), the prevalence of TB CAP in those presenting with acute LRTI was approximately 14%.[12] Notably, *M. tuberculosis* was the most common pathogen associated in those with CAP with *Streptococcus pneumoniae* being the second most frequent. In a report on CAP from a tertiary center in Durban, South Africa (study HIV prevalence rate of 81% and involving 430 participants), *M. tuberculosis* was the causative pathogen in 40% of HIV-infected and 35% of HIV-uninfected persons.[13] Again, *M. tuberculosis* was the most frequent pathogen isolated with *S. pneumoniae* being the second most frequent pathogen isolated. A study in Botswana recruiting 1,305 patients found the prevalence of TB CAP to be 5.2% (87% of those with CAP were HIV-infected).[14] Similarly, a study in Kenya found the prevalence of TB CAP to be 9%, and 52% of those with CAP were HIV-infected.[15]

In non-HIV-endemic areas there is also an appreciable prevalence of CAP in those presenting with acute LRTI. For example, a study from Hong Kong that enrolled 1,193 participants who were HIV-uninfected, found the prevalence of TB CAP in acute LRTI to be 8.1%.[16] A study from the rural Philippines that recruited 535 patients found the prevalence of TB CAP to be 9.8%,[17] and prospective multicentric studies from Cambodia and Vietnam (but in HIV-infected persons) found a TB CAP prevalence of 20 and 19%, respectively.[18] By contrast, in a low HIV prevalence setting like Iran, 17.5% of 120 participants who presented with acute LRTI were found to have TB CAP.[19]

A systematic review involving children, mainly from TB-endemic countries, found that the TB CAP prevalence rate was 7.5% among 7,045 participants.[20] A systematic review interrogating the bacterial etiology of CAP in Asian adults that included 10,423 patients from 48 studies found that gram-negative bacilli and *M. tuberculosis* were more important pathogens with *S. pneumoniae* being of less relative importance[21]; by contrast, in north east Thailand *Burkholderia pseudomallei* was a major pathogen.[22] The authors highlighted that these epidemiological findings have major implications for the local selection of diagnostic and empirical treatment strategies of CAP. They further concluded that narrow-spectrum antibiotics targeting *S. pneumoniae* may be inappropriate in many Asian settings.

## Pathogenesis

The pathogenesis of TB CAP is poorly understood but probably represents an endpoint of different immunopathological trajectories including (1) acute progressive TB pneumonia, (2) superadded infection with bacteria or viruses in those with subclinical TB, and (3) initial bacterial or viral pneumonia with increased susceptibility to and superimposed infection

**Table 1** Prevalence of TB CAP

| Country/region | Total number of participants | Prevalence of TB CAP (%) | Comment | Reference |
|---|---|---|---|---|
| Pietermaritzburg, South Africa[a,b,c] | 8,032 | 14 | HIV and TB endemic setting | 12 |
| Botswana[b] | 1,305 | 5.2 | HIV and TB endemic setting. 87% of CAP HIV-infected | 14 |
| Durban, South Africa[a,b,c] | 430 | Overall: 39.6<br>40 in HIV +ve<br>35 in HIV −ve | Consecutive patients over a 17-month period.<br>HIV and TB endemic area | 13 |
| Kenya[a,b,c] | 281 | 9 | 52% of CAP HIV infected | 15 |
| Cote d'Ivoire | 200 | 61 | Cross-sectional study of HIV-infected patients with CAP | 11 |
| Central African Republic[a,b] | 101 | 60 | Prospective multicenter study in HIV-infected persons with smear negative sputum | 18 |
| Cape Town, South Africa[a,b,c] | 81 | 6 | Prospective CAP study over 5 months | 124 |
| Senegal | 70 | 24 | Prospective multicenter study in HIV-infected persons with smear negative sputum | 18 |
| TB endemic areas | 7,045 | 7.5 | Systematic review in children | 20 |
| Hong Kong | 1,193 | 8.1 | Prospective study of non-HIV-infected CAP | 16 |
| Hong Kong | 90 | 12.2 | Prospective study of non-HIV-infected CAP | 26 |
| Pan Asia | 955 | 3.3 | Prospective surveillance of CAP in 8 countries | 125 |
| Philippines[a,c] | 535 | 9.8 | Prospective CAP study | 17 |
| South Korea | 528 | 7 | High TB prevalent suburban area | 35 |
| Japan | 349 | 1.7 | Prospective CAP study | 126 |
| Japan | 326 | 1.5 | Prospective CAP study | 127 |
| Malaysia | 346 | 4.9 | Prospective CAP study; HIV testing not performed | 3 |
| Malaysia | 108 | 10.2 | Prospective CAP study | 128 |
| Malaysia | 98 | 15.3 | Prospective CAP study; HIV-infected persons excluded | 129 |
| India[a,b,c] | 233 | 5.1 | Prospective study of CAP | 130 |
| China,[a,b,c] Beijing | 197 | 1 | Consecutive outpatient recruitment of CAP | 10 |
| Cambodia | 193 | 20 | Prospective multicenter study in HIV-infected persons with smear negative sputum | 18 |
| Taiwan | 168 | 1.2 | Prospective CAP study | 131 |
| Taiwan | 100 | 2 | Prospective CAP study | 132 |
| Iran | 120 | 17.5 | Low HIV prevalence setting | 19 |
| Thailand[a,c] | 119 | 2 | Hospitalized CAP including HIV-infected persons | 22 |
| Vietnam[a,c] | 98 | 19 | Prospective multicenter study in HIV-infected persons with smear negative sputum | 18 |
| Singapore | 96 | 21 | Prospective CAP study | 133 |

Abbreviations: HIV, human immunodeficiency virus; CAP, community-acquired pneumonia; MDR, multidrug resistant; TB, tuberculosis.
[a]High TB burden country by absolute number.
[b]High TB-HIV burden country by absolute number.
[c]High MDR-TB burden country by absolute number.

with *M. tuberculosis*. In TB-endemic countries, approximately 1 to 2 percent of the population in informal settlements and shanty towns may have active TB.[23–25] Consequently, in some cases, acute LRTI may precipitate clinical presentation with recovery of *M. tuberculosis* during investigation but failure to culture or identify the relevant viral or bacterial pathogen. Recovery of more than one pathogen in those with TB CAP supports this hypothesis. Indeed, in various TB CAP-associated studies, co-infection with different organisms including influenza, *S. pneumoniae*, and *Acinetobacter/Enterobacter* was noted in 1, 14.3, and 9% of patients, respectively.[12,13,26] It remains unclear if the recovered organisms were colonizing bystanders or represented disease-causing entities, thus contributing to hypoxia and the clinical features at presentation. It is likely that both possibilities are tenable. The interaction between bacteria such as pneumococcus, *Haemophilus influenzae* and viruses like influenza, and increased susceptibility to TB with accelerated presentation remain unstudied. However, in a phase 3 study with almost 40,000 participants, pneumococcal vaccination was associated with a 40% reduction in culture-

confirmed TB among hospitalized vaccinated patients compared with those who remained unvaccinated over a 5.3-year follow-up period.[27] It is possible that the pneumococcal vaccination prevented bacterial superinfection in TB cases or alternatively may have acted through reducing enhanced susceptibility (it is likely a combination of these possibilities).

Alternatively, *M. tuberculosis* may rapidly progress and present as lobar consolidation and pneumonia. This type of presentation, sometimes referred to as progressive primary disease, is more commonly seen in children but may also be seen in adults.[28] Reasons for rapid progression of TB to lobar consolidation and pneumonia-like presentation with lack of granuloma containment are poorly understood. However, it is likely related to genetic and acquired immune dysfunction that fails to contain *M. tuberculosis* and retard disease progression. Clinical experience and published data suggest that autophagy, CD4 T-cells, CD8 T-cells, tumor necrosis factor (TNF)-α, regulatory T-cells, and other mycobactericidal mechanisms (including granzyme, cathelicidin, and the vitamin D pathways) are likely to be important in protecting against *M. tuberculosis*; however, a clear-cut protective biosignature has, hitherto, not been clarified.[29,30] Thus, the immunopathogenesis of TB is poorly understood and there are no well-accepted correlates of protective immunity. It is likely that immune paresis is the likely mechanism as TB CAP is more common in HIV-infected persons (and in those with advanced immunosuppression), and HIV co-infection increases susceptibility to TB and accelerates progression through subversion of macrophage and CD4 T-cell responses.[31]

Other factors that could influence presentation and the evolution to TB CAP, compared with the more indolent presentation of apical cavitary disease, may include strain type, the force of infection or intensity of exposure, and host–pathogen interaction, i.e., inflammatory response at the level of host-adaptive immunity.[32]

## Clinical Presentation

TB CAP may be difficult to differentiate clinically from non-TB pneumonia (non-TB CAP) on clinical and radiological grounds.[26] This results in delay in the diagnosis of TB thus increasing not only morbidity and mortality but also the nosocomial and nonnosocomial transmission of TB.[33] However, can clinical and radiological features help distinguish TB CAP from non-TB CAP? In a multivariate analysis of 6,976 patients hospitalized with CAP (TB CAP and non-TB CAP), Cavallazzi and colleagues derived five independent predictors of TB CAP, i.e., night sweats, hemoptysis, weight loss, *M. tuberculosis* exposure, and upper lobe infiltrate.[34] Similarly, Chon et al, in a study with TB CAP prevalence of 7%, identified symptoms >7 days, upper lobe involvement, night sweats, cavitary/nodular infiltrates, and a serum albumin <3.5 g/dL as independent predictors of TB. Two or more factors had a sensitivity and specificity of 81.1 and 75.8% respectively with a positive predictive value of 24.4% (if at least two of these factors were present) and a negative predictive value of 97.9% (if none of these factors were present).[35] In addition, longer duration of symptoms, leucopenia, and lymphopenia were also predictive of TB CAP.[3,36] A pleural effusion and upper lobe involvement were the radiographic features more commonly seen with TB CAP.[26] A course of antibiotics with assessment of clinical and radiologic response was found to be better than derived scores in predicting TB CAP. In one study, a failure to respond to a course of amoxicillin had a positive predictive value of 91% and a negative predictive value of 94%.[37]

## Tuberculosis in the Critically Ill and the ICU

A diagnosis of TB in the intensive care unit (ICU) in TB-endemic countries is not uncommon. However, there may be different categories of TB patients admitted to the ICU. A subset may be admitted to the ICU because of TB CAP. Alternatively, patients may have had prior active TB and are then admitted to the ICU because of sepsis or other complications, or TB may have been incidentally discovered in patients admitted to the ICU for unrelated reasons, e.g., trauma (subclinical TB), and rarely due to disseminated TB-associated acute respiratory distress syndrome.[38] Thus, the most common indication for TB-related ICU admission is acute respiratory failure or multiorgan failure; however, often, these complications may not be directly related to TB.[38–42] Other potential indications for ICU admission are massive hemoptysis, cardiogenic shock, and neurological deterioration in patients with tuberculous meningitis.[38,43–45] Thus, there are no data specifically on TB CAP and outcomes in the ICU; this is an area that warrants further study. Nevertheless, in our experience, the mortality rate remains high in patients with TB CAP requiring mechanical ventilation and is estimated to be twice as high as non-TB CAP requiring mechanical ventilation.[45] A mortality rate of 69% was noted in a Canadian study of TB patients requiring mechanical ventilation.[46] Similarly, a high mortality rate of 65.9% was recorded by Lee and colleagues at a tertiary hospital in Taiwan in patients with active TB requiring mechanical ventilation.[45] A retrospective review in Germany recorded a mortality rate of 22.4%, which is similar to that of non-TB CAP requiring mechanical ventilation.[44] More recently, in a prospective study in a TB-endemic setting, Calligaro and colleagues reported ICU mortality of 27% and in-hospital mortality of 31% at a tertiary hospital in Cape Town, South Africa.[38] In this study, patients with known prior active TB requiring ICU admission were analyzed separately. Importantly, they observed that mortality in patients diagnosed with TB in ICU was no different to that of other critically ill patients without TB. However, in the same city but in a different ICU, Balkema et al prospectively enrolled active and subclinical TB patients and reported an ICU and in-hospital mortality of 44.2 and 59%, respectively.[43] Mortality rates of 22 to 70% have been observed in TB–HIV co-infected patients admitted to the ICU.[41,42,47]

In summary, risk factors associated with increased mortality in ICU (and not specifically due to TB CAP alone) include older age, mechanical ventilation, multiorgan failure, APACHE II score of >20, hemodynamic instability requiring vasopressors, nosocomial pneumonia, and delayed initiation of antituberculous treatment.[38,43–45,47] In

addition to the above risk factors, advanced immunosuppression, hypoalbuminemia, and lymphopenia are predictors of increased mortality in TB–HIV co-infected patients in the ICU.[41,42,47]

## Diagnosis of TB CAP

### The Challenge of Biological Sample Acquisition

Most of the diagnostic tests for TB rely on expectoration of a good sputum sample. Some patients may not be able to expectorate sputum. Indeed, 64% of HIV-uninfected persons with non-TB CAP are sputum scarce.[48] In HIV-infected patients with pulmonary TB in general (not specific to TB CAP), up to a third of patients are unable to produce sputum for diagnostic testing.[49] In addition, in this subgroup the bacillary load in the sputum is low and thus, a significant proportion are sputum smear negative.[50–52] We have demonstrated that sputum induction and bronchoalveolar lavage aid sputum acquisition in smear-negative and sputum-scarce patients with good results and should be used when appropriate.[53–55] Tracheal aspirates from patients on mechanical ventilation have also been shown to yield good results.[38] In summary, when test results are negative, this may be due to sampling error, i.e., poor quality sputum, and thus teaching patients how to properly expectorate sputum is important.

### Nonspecific Discriminatory Biomarkers Distinguishing TB CAP from Non-TB CAP

As outlined, differentiating TB CAP from non-TB CAP on clinical and radiologic grounds is often challenging. However, procalcitonin (PCT) and C-reactive protein (CRP), which are markers of inflammatory response to infection, differ significantly between TB CAP and non-TB CAP. PCT and CRP are generally significantly higher (both in HIV-infected and uninfected persons) in bacterial/non-TB CAP than in TB CAP with sensitivity ranging from 43 to 87% for PCT and 78 to 83% for CRP, while specificity for PCT ranged from 78 to 88% and that for CRP from 75 to 83%. Positive and negative predictive values for PCT ranged from 65 to 67% and 74 to 91%, respectively, while that for CRP from 64 to 82% and 65 to 89%, respectively.[56–59] These values although broadly discriminating fail to achieve thresholds that make them useful for clinical practice (would rule in or exclude only roughly two-thirds of individuals). Yoon and colleagues identified a neutrophil-to-lymphocyte ratio $<7.0$ as the optimal cut-off value for distinguishing patients with TB CAP from patients with bacterial non-TB CAP, yielding 91.1% sensitivity, 81.9% specificity, 85.7% positive predictive value, and 88.5% negative predictive value.[60] The triggering receptor expressed on myeloid cells (TREM)[61] is a recently described member of the immunoglobulin superfamily expressed on blood phagocytes and alveolar macrophages. TREM-1 is selectively expressed in the lungs of patients with bacterial non-TB CAP and not in TB CAP.[61] Further studies are needed to clarify its utility in distinguishing TB CAP from other causes of CAP.

### Confirmatory Microbiological Tests for *M. tuberculosis* (►Fig. 1)

Confirmation of a TB diagnosis is challenging. Globally, only just over 50% of TB is microbiologically confirmed.[62] In most

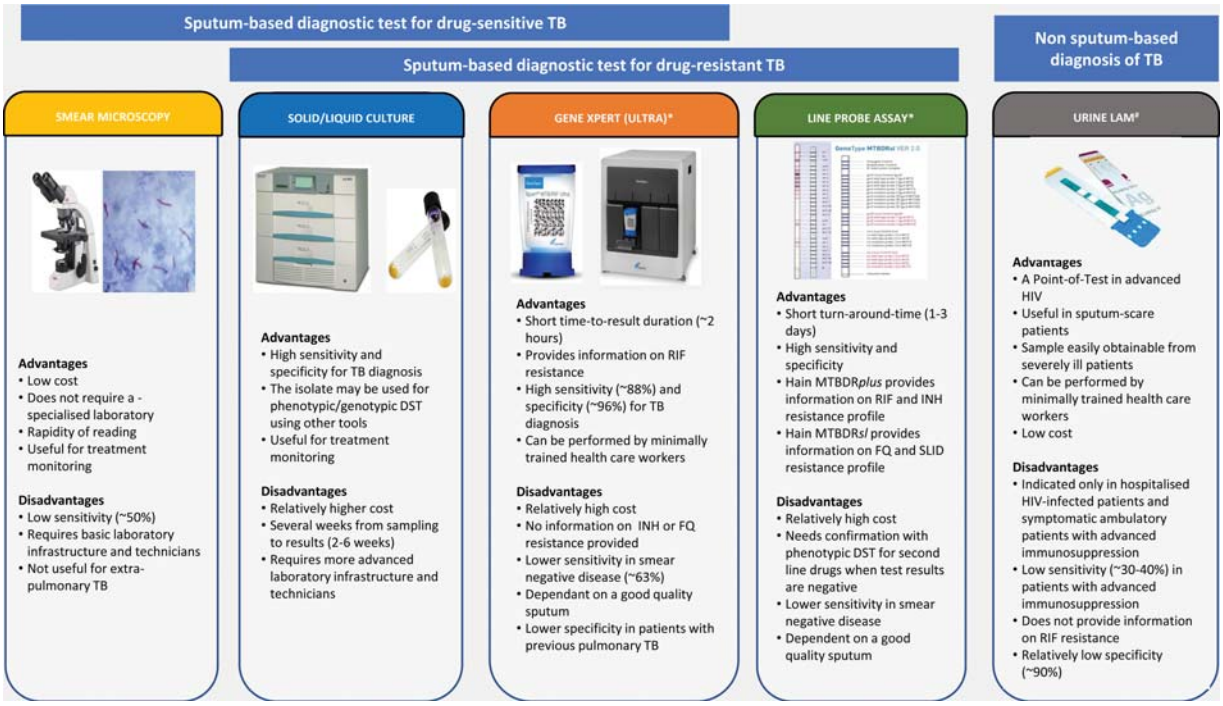


**Fig. 1** Currently available sputum and urine-based tools for the microbiological diagnosis of drug-sensitive and drug-resistant tuberculosis. *The WHO-approved Cepheid GeneXpert MTB/RIF and Hain Lifescience line probe assay have been depicted but other nucleic acid amplification tests (NAAT) such as Amplified Mycobacterium Tuberculosis Direct (MTD) test by Gen-Probe Inc., and Amplicor Mycobacterium Tuberculosis Test by Roche Molecular Systems are also FDA-approved and commercially available. DST, drug susceptibility testing; FDA, Food and Drug Administration; FQ: fluoroquinolones; INH, isoniazid; RIF, rifampicin; SLID, second-line injectable drugs (e.g., kanamycin and amikacin).

high TB-burden settings, despite the advent of molecular diagnostics, smear microscopy remains the standard of care though the sensitivity is only approximately 50%.[63] The sensitivity of same-day smear microscopy can be improved by approximately 10% after sample centrifugation and use of fluorescence microscopy.[64] The quasi-gold standard confirmatory test is automated liquid culture, which has a limit of detection of approximately 10 organisms per mL and is more sensitive. However, it is more costly and more prone to contamination than solid media.[65,66]

Nucleic acid amplification tests are now available as confirmatory tests and the WHO has endorsed the use of the Hain MTBDRplus and MTBDRsl assays and Gene Xpert MTB/RIF, now superseded by Xpert Ultra, for the diagnosis of TB.[67] In a multicentric study, Xpert Ultra had a sensitivity of 97.8% in smear positive, 78.9% in smear-negative pulmonary TB, with high specificity and a level of detection in sputum of 15.6 organisms/mL.[68] By contrast, the sensitivity of Xpert is suboptimal in TB serositis (pericarditis, pleural and peritoneal TB).[69,70] Although Xpert assays are cost-effective and enable rapid detection of rifampicin-resistant TB, they are unable to detect isoniazid monoresistant TB, might remain positive for several years after completion of treatment (therefore often positive in those with previous TB),[53,71] and cannot be used to monitor treatment.[72,73] Furthermore, although Xpert enables a more rapid diagnosis, it failed to show a clear-cut reduction in morbidity, mortality, and impact on the burden of TB.[74–76] The latter is not surprising given that most TB transmission (>95%) has occurred prior to patients presenting to health care facilities for treatment.

Alternative confirmatory susceptibility testing is advisable in regions where MDR TB prevalence is less than 10% because of the modest positive predictive value of Xpert or rifampicin resistance.[67] Genotypic resistance testing beyond rifampicin, including second-line drugs, may be undertaken using multiplex molecular assays, e.g., the Hain MTBDRplus and MTBDRsl using TB isolates or smear-positive sputum.[77] Targeted or next-generation sequencing is being investigated but the technology is not yet ripe for use in clinical practice and its impact on treatment outcome still needs to be established.[78] However, as technology improves, next-generation sequencing has great potential for rapid diagnosis of drug-resistant TB in diverse clinical settings once several hurdles are overcome.[79]

The urine lipoarabinomannan (LAM) point-of-care lateral flow assay is a useful low-cost test in patients with advanced HIV, especially in those with CD4 count less than 100 cells/mL and particularly in patients who are sputum scarce. Even in this group, although sensitivity is only approximately 30 to 40%, its use in HIV-endemic settings has demonstrated a mortality benefit.[49] LAM sensitivity increases with decreasing CD4 count.[49,80]

In summary, in TB and HIV high- and intermediate-burden settings where TB CAP comprises a significant proportion of all patients with CAP, patients should be routinely tested for TB. Molecular, microscopic, antigen-based, and culture-based testing should be used depending on the clinical and situational context. This has a bearing on morbidity and mortality as well as nosocomial transmission of TB to health care workers and patients without TB.[81,82] Finally, to confirm the diagnosis and direct therapy, appropriate ancillary testing for other causes of CAP should be undertaken including tests for *Pneumocystis jirovecii* (PJP), viruses, fungi (including PJP), and bacteria (including blood and sputum culture, and serological and antigen-based testing for *Legionella* and atypical bacteria).

## Clinical Management of TB CAP

Treatment of TB CAP is generally no different from treatment of other forms of TB.

### Drug-Sensitive TB

The current 6-month regimen for drug-sensitive TB was derived in the 1970s and is still highly effective. Given the long duration of therapy treatment, default rates can be substantial.[83] African patients on TB treatment had delayed lower sputum conversion rates,[84] likely as a result of lower levels of rifampicin in Black Africans[85] related to drug metabolism by liver enzymes, e.g., there is a high frequency of a polymorphism in SLCO1B1 gene.[86] To improve adherence, directly observed therapy (DOT) was widely implemented. However, a meta-analysis has shown that DOT is no better than self-administered therapy in preventing microbiologic failure, relapse, or adverse drug reactions.[87] Drug-induced liver injury is the most serious side effect of treatment.[88]

### Adjunctive Corticosteroids for TB CAP

Adjunctive steroid use remains controversial in TB CAP as it is in non-TB CAP.[89,90] There is no proven indication for steroids in TB CAP unless the patient has concomitant tuberculous meningitis where steroids reduce death and neurological deficit, or tuberculous pericarditis where a mortality benefit was noted.[91,92] However, a large study done in South Africa evaluating efficacy of steroids in tuberculous pericarditis did not show a mortality benefit, though there was a reduction in the development of constrictive pericarditis.[93] Adjunctive steroids are also indicated in patients with severe TB CAP requiring vasopressors and/or with adrenal insufficiency.[94] The downside of steroid use includes gastrointestinal bleeding, hyperglycemia, exacerbation of immune paralysis, and superinfection,[95] and increased incidence of cancer in HIV-infected patients who are not on antiretroviral therapy.[93] Thus, use of steroids in TB CAP must be individualized and is clinical-context-dependent.

### Therapeutic Drug Monitoring

It has now been established that the pharmacokinetics of anti-TB drugs is influenced by several factors including patient demographic profile including age, sex and ethnicity, gastrointestinal motility, drug formulation, and co-administration with other drugs leading to drug–drug interactions.[96–100] The recommended rifampicin dose of 10 mg/kg, derived in the 1970s, was based mainly on perceived high cost and toxicity considerations. Several studies have consistently shown that lower than expected maximal drug concentrations was associated with a poor clinical outcome.[96,100–102] More

recently, clinical studies of high-dose rifampicin, up to 35 - mg/kg, demonstrated that it was associated with improved pharmacokinetics, and higher early mycobactericidal activity. Thus, rifampicin-based therapeutic drug monitoring (TDM)[100] is likely beneficial in certain patient subgroups such as those who have poor prognostic features (and are thus slow to respond to treatment), including HIV-infected persons, those at risk of drug–drug interactions, in those with likely altered drug pharmacokinetics, and in those with DR-TB.[100] Controlled trials on the impact of rifampicin-based TDM are eagerly awaited.

Little is known about the pharmacokinetics of anti-TB drugs in the ICU since it is modulated by several factors, including enteral nutrition, gastroparesis, intestinal paralysis, ulcer prophylaxis, and liver and renal dysfunction.[103] Indeed, preliminary findings by Koegelenberg and colleagues showed that crushed fixed combination tablets given via a nasogastric tube to TB patients in ICU was associated with subtherapeutic levels of rifampicin especially in patients with higher APACHE II scores.[104] This could be circumvented by giving anti-TB drugs intravenously. However, only rifampicin and isoniazid are available as intravenous injections.[104] Given the above-mentioned considerations, we recommend the use of rifampicin-based TDM in appropriate patients including those with TB CAP and in the ICU.

### Treatment in TB–HIV Co-infected Patients

Recurrence of TB, generally from reinfection rather than reactivation, is high in TB-HIV co-infected patients.[105] Rifampicin, which is a hepatic inducer of drug-metabolizing enzymes and transporters, may lower concentration levels necessitating increased doses of antiretroviral drugs or switching to rifabutin, a weaker hepatic inducer.[1] Immune reconstitution inflammatory syndrome (IRIS)[22] is an immunopathological response usually seen at least 2 weeks after initiation of antiretroviral therapy that may unmask TB or paradoxically worsen TB manifestations. The risk of TB-IRIS increases with falling CD4 count and is associated with a low mortality.[106] Oral prednisone reduced the need for hospitalization and therapeutic procedures, and hastened improvement of symptoms in patients with TB-IRIS.[107] In addition, prednisone lowered the incidence of TB-IRIS.[108] The same considerations are likely to apply to TB CAP.

### Management of TB CAP that Is Resistant to Frontline TB Drugs

Two new drugs, bedaquiline and delamanid, have been registered for use in DR-TB. Several other drugs including later generation of fluoroquinolones, linezolid, and clofazimine have been repurposed for the treatment of DR-TB. The WHO has now newly grouped second-line drugs into Group A (bedaquiline, fluoroquinolone, and linezolid), B (clofazimine, cycloserine/terizidone), and C that include all the remaining agents based on their impact on mortality and treatment-related outcomes. Till recently, treatment success rates for DR-TB have been only approximately 50%,[109] and the regimens have been toxic, poorly tolerated, and prolonged.

When treating rifampicin-resistant TB the WHO advises that all three Group A agents and at least one Group B agent should be included to ensure that at least four effective drugs are used (ideally, we recommend that at least five likely effective drugs should be used). A total treatment duration of 18 to 20 months is suggested for most patients depending on time to culture conversion, though in some settings like South Africa shorter regimens are routinely being used. Sputum culture and microscopy can be used to monitor treatment response. The emergence of programmatically incurable TB and discharge back into the community of such patients has raised legal, ethical, and logistical dilemmas in high-burden settings as these patients remain infectious.[110,111]

## Prognosis and Outcome of TB CAP

In non-TB CAP, mortality varies between $<1\%$ and nearly 50% depending on disease severity, initiation of timely appropriate treatment, and other factors.[18,112] By contrast, mortality rates in TB CAP are reported to be between 7 and 70% depending on severity and prognostic factors.[18,43,47,113] In a study conducted at a tertiary center in Durban, South Africa, the overall mortality for CAP was 17% (15.7 and 26.7% in HIV-infected and uninfected groups, respectively). In those with TB CAP, mortality in the HIV-infected and uninfected groups was 26 and 11%, respectively. In the same study in those with pneumococcal pneumonia, mortality in the HIV-infected and uninfected groups was 18 and 22%, respectively.[13]

## Post-TB CAP Complications and Post-TB Lung Disease

Pulmonary TB causes substantial chronic morbidity due to lung remodelling[32] resulting in chronic pulmonary obstructive disease,[114] posttuberculous bronchiectasis, *Aspergillus*-associated lung disease, and lung destruction.[32] Those with TB CAP are at risk of the same sequelae though little is known about the nature of post-TB lung disease (PTBLD) in TB CAP versus more indolent forms of TB. PTBLD causes progressive disability and may be complicated by respiratory failure and/or massive hemoptysis requiring either surgery or bronchial artery embolization. The pathogenesis of PTBLD is poorly understood but may result from dysfunctional extracellular matrix deposition and clearance.[32] Aspergillomas in the residual cavities may cause massive hemoptysis or chronic pulmonary *Aspergillus*-associated disease.[115]

## Prevention of TB CAP

There is currently no proven population-wide effective vaccine for TB though a recent phase III trial showed promising results.[116] Bacille Calmette-Guerin (BCG), which is still administered at birth in most TB-endemic countries, provides approximately 30% protection against TB in adults[117] and protects against disseminated form of TB, like TB-meningitis in children.[118] There is circumstantial evidence that vaccination

against *S. pneumoniae* and influenza may afford some protection against *M. tuberculosis* and conversely that BCG may provide protection against LRTI through the mechanism-trained innate immunity.[119] Identification and treatment of latent TB infection (LTBI) is an important preventative strategy that is used in certain high-risk groups in low-burden settings[120] and in HIV-infected persons and children under 5 years in resource-poor settings.[121] However, it is now recognized that TB will never be eradicated without treating LTBI, which can later spawn cases of active TB driving ongoing community-based transmission. Hence, recent WHO guidelines have for the first time conditionally approved identification and treatment of LTBI in HIV-uninfected close contacts of index cases in TB-endemic settings.[122] In sub-Saharan Africa and other appropriate settings, universal testing for HIV (or in certain high-risk groups) with provision of antiretroviral therapy is an important preventative measure given that HIV is a potent risk factor for TB. Epidemiologically, at a population-based level, cigarette smoking and biomass fuel exposure are even bigger drivers of TB than HIV.[1] Thus, smoking cessation and public health interventions to minimize exposure to biomass fuels are an important preventative strategy. Similarly, awareness campaigns and public health strategies educating people about TB, TB CAP, and non-TB CAP, including awareness about the symptoms and risk factors for TB, are important. It is remarkable that two out of every five TB cases globally remain undetected![62] Thus, community-based active case finding is a critical preventative strategy to reduce the burden of TB in general. Passive case finding (where patients self-seek medical care) is currently the dominant public health strategy employed globally. However, with this approach more than 95% of transmission has already occurred prior to treatment initiation. Newer portable molecular tools that can be used at point of care[23] including development of new screening tools[123] promises to revolutionize community-based active case finding for TB.

## Conclusion

TB CAP is more common than appreciated and is an important cause of acute LRTI in Africa, Asia, and South America. TB should be considered as part of the differential diagnosis and should be specifically excluded in patients with CAP in these settings. In low TB-burden settings, TB CAP should be considered in high-risk groups including immigrants, HIV-infected persons, and those with immunosuppressive conditions including chronic organ dysfunction. Our ability to rapidly diagnose TB has markedly improved and in countries like South Africa, rapid molecular assays are frontline tools that are available in almost every primary level clinic. Drug-sensitive TB treatment is generally associated with good outcomes and there is considerable work being undertaken to find shorter and more effective treatment regimens. Although there is no effective vaccine, treatment of LTBI in appropriate settings and implementation of basic preventative measures such as BCG vaccination, HIV testing and treatment, smoking cessation, and reduction in exposure to biomass fuels are important preventative strategies. However, until there is greater alleviation of poverty and overcrowding, improved research funding, and improved political will, TB, non-TB CAP, and TB CAP will continue to be important causes of morbidity and mortality, particularly in resource-poor settings.

Conflict of Interest
None declared.

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