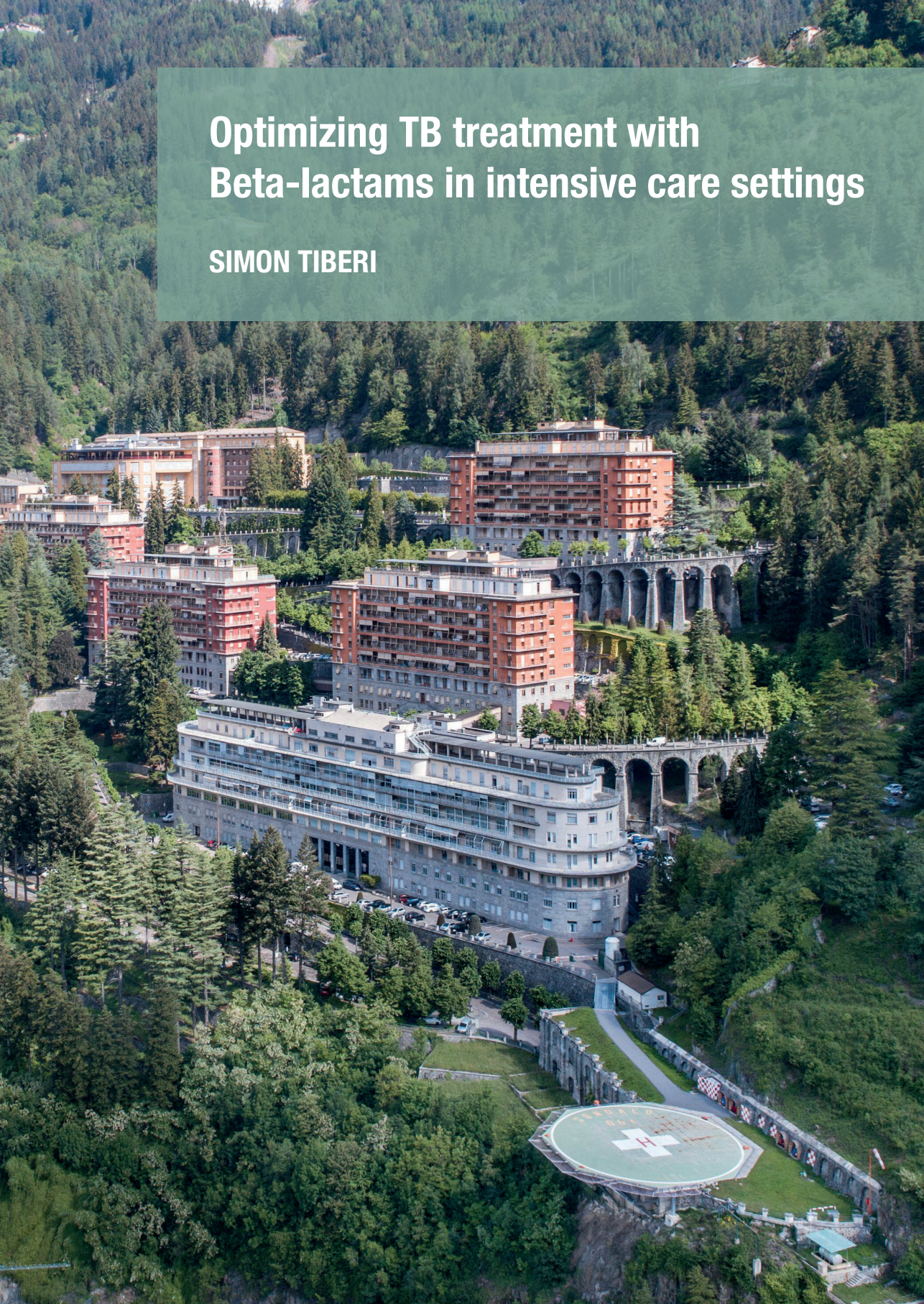
Optimizing TB treatment with Beta-lactams in intensive care settings

SIMON TIBERI



PROPOSITIONS

related to the thesis

Optimizing TB treatment with Beta-lactams in intensive care settings

1. Current tuberculosis treatment paradigms underestimate the potential role of β-lactams in shortening and simplifying therapy.
2. Meropenem/clavulanate containing regimens are more effective and equally safe compared to imipenem/clavulanate for treating multidrug and extensively drug resistant tuberculosis.
3. The apparent superiority of meropenem/clavulanate over imipenem/clavulanate reflects true pharmacological advantage rather than confounding by indication.
4. Meropenem/clavulanate should be used more frequently in less severe drug resistant tuberculosis, not only as salvage therapy.
5. The lower observed effectiveness of imipenem/clavulanate is primarily due to its use in more severe MDR/XDR-TB cases, rather than through inferior intrinsic efficacy.
6. Diagnosis and treatment of tuberculosis in the intensive care unit remains underdeveloped and contributes directly to excess mortality.
7. Early initiation of intravenous anti-TB therapy in critically ill patients will reduce mortality, even if definitive evidence is currently lacking.
8. Pulmonary TB in ICU is associated with high mortality, highlighting the need for earlier diagnosis, tailored scoring systems, and intravenous anti-TB therapy.
9. Total eradication of tuberculosis would significantly improve global health but is impossible without addressing underlying socioeconomic issues.
10. "It is clear from these observations that in the cellular substance of the molds examined are contained some water-soluble substances, provided with bactericidal action." *(Vincenzo Tiberio, 1895 on beta-lactams)*
11. "Tuberculosis is a disease of poverty, but it knows no social or economic boundaries." *Phil Loper*
12. "Life is a sexually transmitted disease and the mortality rate is one hundred percent." *R. D. Laing*
13. We often rediscover old truths and go back to where we once were, β-lactams in tuberculosis are a prime example.
14. Hope is the last thing to die, yet in treating tuberculosis, hope must be paired with early action to have the most value.
15. In TB we are not waiting for solutions but rather we are waiting to use them!

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Simon Tiberi

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Optimizing TB treatment with Beta-lactams in intensive care settings

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Chapter 1

General introduction

Tuberculosis (TB) is an airborne infectious disease caused by *Mycobacterium tuberculosis* (Mtb) a non motile, non spore forming bacillus of the Mycobactericeae family and transmitted through bacilli-containing aerosol droplets typically through sneezing or coughing.[1] After exposure to *Mtb*, an estimated 20–25% of people exposed become infected. Amongst those infected, 5–10% will go on to develop active disease, while 90% control the replication of the pathogen. Reactivation occurrs in around 5% within 2 years of infection and a further 5% reactivate later.[2] TB is prevalently a pulmonary disease, but TB can affect any organ of the body. The likelihood of developing the disease or reactivating it increase with comorbidities such as co-infection with human immunodeficiency virus (HIV), diabetes mellitus, malnutrition, treatment with immuno-suppressive therapy, such as glucocorticoids or biological agents, solid organ transplantations, malignancies, and genetic predisposing factors.[3] Certain lineages of TB may have different clinical phenotypes, for example the virulent Lineage 2, may be more inclined to cause pulmonary disease than others.[4]

In 2024 1.23 million people died from TB, making it the leading infectious diseases killer in the world and the main cause of death for people living with HIV according to the World Health Organization (WHO), 2025 Report.[5]

TB is curable and preventable. The currently available BCG only prevents the more severe forms in neonates and young children.[6]

The current long-standing first-line anti-TB agents despite their successful rollout 4 decades ago have not been completely effective in controlling the TB epidemic in high-burden countries due to the overlap with the HIV pandemic, their poor tolerability and lack of forgiveness with compliance below 90%.[7,8] Treatment for drug-susceptible TB takes 4–6 months to complete and is associated with side effects resulting in poor adherence which can lead to treatment failure and an increased likelihood of developing drug-resistance.[9]

Drug-resistant TB poses a major threat to control of the TB epidemic and one of the major challenges to TB control and elimination efforts. The prevalence of multi drug-resistant TB (MDR: resistance to at least isoniazid and rifampicin) and extensively drug-resistant (XDR: MDR plus resistance to at least a fluoroquinolone and either/both bedaquiline and linezolid) continues to increase.[10] Really concerning is resistance to new drugs that took decades to develop, but is rising at an alarmingly rapid pace since instituting bedaquiline as standard of care.[11] The WHO estimates that 3.2% of new and 16% of previously treated TB cases occurring worldwide in 2023 had MDR-TB, which translates into close to half a million new cases of MDR-TB.[5]

Current management of drug-susceptible (DS) TB

All TB cases with DS-TB forms require treatment using the primary 6-month combination regimen including four first-line TB drugs [Isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E)].[12] This HRZE regimen has produced extraordinary gains, averting 83 million deaths since 2000.[13] About 80–85% of people developing DS TB disease can be successfully treated with this regimen under current programme conditions, while clinical trials with their intensive follow-up and incentivisation of treatment completion show higher cure rates, up to 95%.[13]

Treatment success with the current HRZE treatment regimen is very reliant on treatment adherence, as shown in a meta-analysis of clinical trials – at sub-maximal compliance of 90–99%, the hazard ratio for unfavourable outcome was 2.4 (95% CI 1.6–3.6) compared to 100% compliance; at ≤90% compliance, it was 5.9 (3.3–10.5) compared to 100% compliance.[14] Achieving such high treatment compliance in a long treatment with tolerability problems like nausea or vomiting can be a challenge, though patients can be supported.[15] Furthermore, the HRZE regimen may cause drug induced liver toxicity in a substantial proportion of patients – between 5 and 33% of patients, this frequently leads to temporary treatment cessation and readjustments in the regimen and seldomly may lead to liver failure and death.[16]

Recently a 4-month regimen with isoniazid, rifapentine, pyrazinamide and moxifloxacin has also been recommended in parallel with the 6-month regimen, but its uptake remains limited because of its high cost, tolerability, lack of a fixed-dose combination and concerns about the use of a fluoroquinolone.[17-19] A shorter and better tolerated treatment for DS-TB would be desirable in order to cure people with TB faster, interrupt transmission rapidly, and achieve a higher treatment completion rate and cure rate. The 2016 WHO target regimen profile updated in 2023 has set an intended duration for a DS-TB regimen at 4 (minimal requirement) to 2 months (optimal requirement).[19,20]

Current treatment of drug-resistant (DR) TB

Rifampicin resistant TB (RR-TB)/MDR-TB is an uncontrolled part within the current TB epidemic. Modelling suggests that 75% of the MDR-TB, and around half of XDR-TB cases are transmitted through infectious TB isolates that already carry the respective drug resistance mutations.[21] This shows the importance of effective MDR/XDR-treatment to not only treat the individual, but to also interrupt transmission.[22]

MDR/RR-TB requires longer regimens (for a period of 6–20 months), a higher pill burden and the use of medicines with a higher toxicity profile. Globally, almost 15% of MDR/RR-TB patients die from the disease, 26% of the deaths being in patients with extensively drug-resistant TB5. Worldwide, 164,545 people with MDR/RR-TB were enrolled on adequate treatment in 2024, a fall of 7% from 2023.[5] This is equivalent to only 42% of people developing MDR/RR-TB being appropriately treated.

Under-detection and the resulting undertreatment are key shortcomings that do not permit control of MDR-TB currently,[5] as exemplified by Kendall et al. who clearly showed that insufficient cure rates are among the main problems in controlling the transmission and spread of MDR-TB.[23,24] Improved detection and a pan-TB regimen (a regimen that can be used for all TB, regardless of resistance profile) could bridge this gap and provide a further treatment option.

Treatment regimens have improved in the recent years; from 18-month treatments that included daily injectables for 8 months, with high toxicity and poor cure rates of around 50%, to more effective, shorter, and recently, injection-free regimens that cure around 80–90% of patients in clinical trials.[25]

In December 2022, the WHO issued a guideline for the treatment for MDR- and pre-XDR (fluoroquinolone resistant) TB with 6–9-month regimens. No change was suggested for XDR-TB.[17] These new MDR-TB and pre-XDR-TB regimens contain bedaquiline (B), pretomanid (Pa) and linezolid (L) 600 mg once daily. For cases with fluoroquinolone susceptible TB, moxifloxacin (M) is added, and the total duration is 6 months regardless of severity.[26]

Unmet medical need – RR/MDR-TB

Linezolid is one of three Group A drugs listed by WHO to be used in priority for the treatment of DR-TB as a constituent of the short duration BPaL(M) regimen.[17] Linezolid has been evaluated in DS-TB,[27] and MDR and XDR-TB patients.[25] However, despite its treatment shortening potential, linezolid is the cause for much of the toxicity of concern in the newly recommended regimens and it is one of the reasons why new drugs are still needed. The ZeNix study reported that with a 600 mg dose daily for 9 weeks, 13.3% of patients develop reversible peripheral neuropathy, increasing to 24% of participants when given over 26 weeks.[28]

Other toxicities of concern have been reported in the treatment of DR-TB, including prolongation of the QTc interval (average prolongation of each drug given in msec), mainly related

with the use of moxifloxacin (6 msec), bedaquiline (12 msec) and delamanid (8 msec), that requires frequent fortnightly then monthly monitoring. In addition, bone marrow toxicity, hepatotoxicity, peripheral neuropathy and ocular toxicity are observed with current treatments and require monthly laboratory monitoring, peripheral neuropathy screening and visual acuity measurements during treatment.[12] The frequent monitoring raises complexity and costs to people with TB and the programmes.

Similar to DS-TB, there is a need for safer regimens that retain efficacy at a shorter treatment duration and require little to no monitoring.

Due to widespread fluoroquinolone resistance in certain areas of the world, and lack of rapid diagnostics to detect fluoroquinolone resistance, more steps are required to protect bedaquiline.[29]

Treatment of extensively drug-resistant (XDR) – TB

XDR-TB has recently been re-defined;[30] as resistance to fluoroquinolones, plus at least one second category A drug, currently bedaquiline or linezolid.[17]

Resistance against bedaquiline has been described. In Moldova, amongst 26 patients (of the 203 MDR patients treated with bedaquiline between 2016–2018) who had available baseline and follow-up isolates, 4 of them, (15.3%) harbored strains whith acquired bedaquiline resistance under therapy.[31] In South Africa, an early adopter of bedaquiline to replace injectables in their programs and with a consolidated surveillance program, baseline bedaquiline resistance prevalence between January 2015 and July 2019 was 3.8% amongst MDR-TB patients started on bedaquiline based regimens, and in 2022 was reported as 7%,[32] and in 2025 a prevalence of 10.4% was reported in South Africa.[33] Genetic events in the Rv0678 gene were associated with phenotypic bedaquiline resistance.[95] Nevertheless, the impact of higher baseline bedaquiline MICs, the presence of Rv0678 based mutations at baseline, and/or increased post-baseline bedaquiline MICs on microbiologic outcomes is still unclear and remains to be further elucidated and importantly rapid tests for bedaquiline resistance are needed.

Two groups studying programmatic data reported higher levels of emerging resistance: the prevalence of bedaquiline resistance increased from 3% in 2016 to 14% in 2021 in Maputo Mozambique, and showed a striking increase over time in Mozambique, where genotypic resistance rose from 3% in 2016 to 14% in 2021.[35] In another observational study conducted in South Africa, out of a total 40 (31%) of 129 patients from an estimated

pool were eligible, three (8%) of 38 patients assessable by phenotypic drug susceptibility testing (DST) for bedaquiline had primary resistance, 18 (47%) gained resistance (acquired or reinfection), and 17 (45%) were susceptible at both baseline and follow-up.[36] Possibly the relative lack of early bactericidal activity and the long half-life of bedaquiline may be driving resistance to this compound in areas where it is used.[36]

Linezolid appears to have a high barrier to resistance as suggested from very low mutation frequencies relative to other anti-TB drugs. Nevertheless, resistance has been reported in long inadequate treatment regimens. The emergence of linezolid resistance in TB treatment programmes is a matter of concern given that the large-scale expansion of linezolid for TB treatment could introduce sufficient selection pressure and the lower doses being suggested without MIC testing and therapeutic drug monitoring.[37-39]

Treatment options for XDR-TB patients are still severely limited, as none of the newly proposed shorter 6- or 9-month regimens (e.g. BPaL) can be used. This means that patients are still subjected to 18–24-month treatment regimens that include old drugs with severe side effects like cycloserine/terizidone (psychiatric), ethionamide and PAS (gastrointestinal) and injectables such as amikacin (no longer in the XDR-TB definition since it may cause deafness and kidney injury) and meropenem/clavulanate.[40]

Unmet medical need – XDR-TB

The WHO target regimen profile has not specifically defined this category, but here the unmet need is clearly the highest due to high mortality rates. A short regimen composed of new drugs without cross-resistance in this highly resistant disease category is required; and improvements over the current standard of care of 18–24-month treatment regimen are urgently needed to stop onward transmission in healthcare settings and the community.

Outlook and unmet need – Pan-TB

The unmet medical need differs for different forms of TB, but a common solution could be a new regimen composed of drugs with novel mechanisms of action, hence little or no pre-existing resistance, that could be used universally to treat all forms of TB, whatever the baseline strains resistant profiles. This type of “universal” regimen has been named “Pan-TB” regimen in the 2023 WHO target regimen profile (TRP) document.[41] It would overcome the need for shorter and safer treatments for DR-TB, and if sufficiently short and safe, provide an option for DS-TB as well as other benefits to people with Tb and programs.[42]

Another potential benefit of a Pan-TB regimen is that it could be a stop gap when technically challenging DST is unavailable, thus allowing treatment to start without delay. A Pan-TB regimen would thus be highly relevant in resource-poor settings, and, in the absence of toxicity, easy to be programmatically implemented. A Pan-TB regimen could be very beneficial in children where confirmation and DST of TB is infrequent and it would allow coverage of drug-resistant disease with only 19% of children with DR-TB appropriately treated (WHO 2024) and reduce mortality which is the highest for all age groups.[5] Of note, the WHO TRP here for adults and children require a treatment duration of 4–6 months, with a cure rate that is non-inferior to the HRZE standard of care in DS-TB patients.[20]

New TB drug and regimen development

The development of new drug combinations that are effective against drug-resistant strains of Mtb, and that have the potential to shorten the duration of TB treatments offers new hope for tackling the TB pandemic. The addition of the relatively new drugs such as moxifloxacin, bedaquiline,[43-45] delamanid,[46] pretomanid,[47,48] and promising new oxazolidinone[49-52] candidates for M/XDR-TB are important steps in that direction. However, questions remain related to how we can best combine these new drugs and those in the pipeline into effective and safe combination regimens.

A new treatment regimen requires at least three different drugs to which no clinical resistance exists. However, antagonism between drugs, for example rifampicin with the new drugs bedaquiline, pretomanid and delamanid,[53] and the additive potential for significant toxicity e.g. QTc prolongation of moxifloxacin,[54] bedaquiline,[55] and pretomanid and most recently hepatotoxicity with pyrazinamide and pretomanid[56] limit the number of possible combinations.

Currently, a number of new drugs are in drug development (diarylquinolines: sudapyridine, TBAJ-876, TBAJ-587; protein synthesis inhibitors: ganfeborole, delpazolid, sutezolid); DprE1 inhibitors: quabodepistat, BTZ-043, TBA-7371), others have successfully achieved proof of concept as anti-TB agents in humans (telacebec, meropenem-amoxicillin/clavulanic acid) or have even achieved registration for treatment of drug-resistant TB (bedaquiline, delamanid and pretomanid) (Figure 1.1).[57]

A 3-drug regimen given for 6 months including bedaquiline, pretomanid and linezolid was approved for treatment of highly drug-resistant TB by the FDA in 2019.[28] BPaL in combination with moxifloxacin (BPaLM) based on the pomising results of the TB-PRACTECAL study[93]

is now recommended for the treatment of RR/MDR-TB.[17] BPaL is now recommended by the WHO for pre-XDR TB.[17] However, important questions related to the best possible use of those agents in combination remain due to substantial toxicity such as the peripheral neuropathy and myelosuppression ascribed to linezolid.[58] High fluoroquinolone resistance, higher MICs to pretomanid in lineage and growing bedaquiline resistance are additional concerns.[59] The need for at least three different drugs with complementary modes of action with an ability to penetrate caseum to treat TB in 6 months particularly in harder to treat individuals and guarantee relapse free cure could be a challenge.[60] This highlights the need for the development of additional new chemical entities that can strike a balance between antituberculosis activity (cidality and ability to sterilise) and safety profiles, that can enable better, shorter, safer new future drug combinations for the treatment of TB.

TB drug development is lengthy and costly. The TB community has continued to add single active drugs to failing regimens, with the risk to lose them shortly after establishing them in new regimens, hence we must learn to use what we have better, optimize doses, repurpose what is available and protect new drugs in robust well tolerated regimens until the advent of an effective TB vaccine. In this thesis, we wanted to focus on beta-lactams.

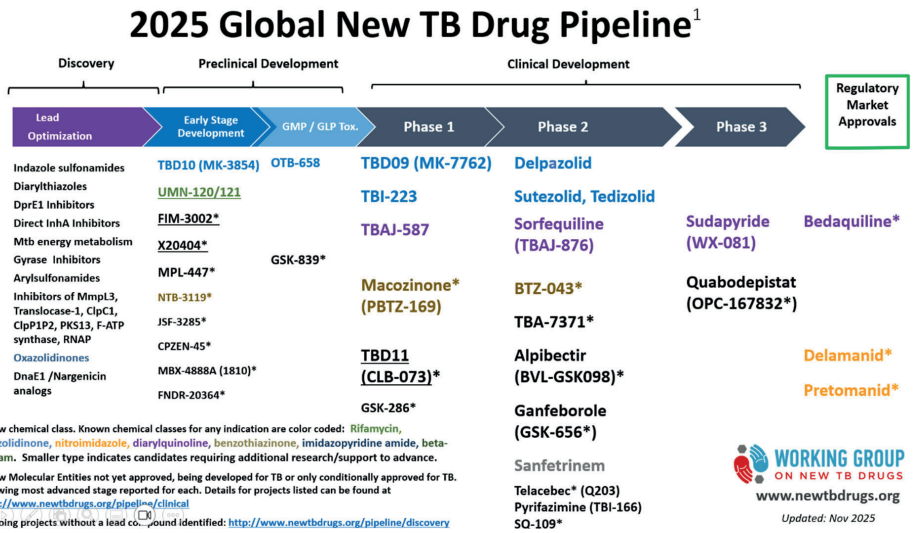


Figure 1.1: 2024 Global New TB Drug Pipeline.[57]
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Beta-lactams for the treatment of TB

The beta (β)-lactams are a well-established large family of antibiotics and antimicrobials that include derivatives of penicillin, cephalosporins, monobactams, carbapenems, and the β-lactam/ β-lactamase inhibitor combinations.[61] The β-lactams are recognised for their clinical safety and have been in widespread use for the past 8 decades.[62] β-lactams act by inhibiting bacterial cell wall synthesis by binding to, and inactivating, the penicillin-binding proteins.[63] β-lactams have since their discovery been the corner stone of antimicrobial therapy and proven to be safe, generally well tolerated and effective.[64] Beta-lactams do not prolong QT interval, have few overlapping toxicities or potential interactions with current antituberculosis drugs and/or antiretroviral agents, are safe in pregnancy and breastfeeding. All this makes them suitable candidates for use in combination treatment regimens in patients with DR-TB and HIV co-infection.[65] Moreover beta-lactams are approved and widely available worldwide.

Early bactericidal activity (EBA) studies are performed to determine whether a compound is intrinsically directly active against MTB or not, in single or combination studies.[66-68] A recent EBA study has reported that meropenem and amoxicillin-clavulanate are active against TB in people with pulmonary tuberculsois.[69] Meropenem however has the inconvenience that it can only be administered intravenously, thrice daily, and should be co-administered with a β-lactamase inhibitor.[70,71] Carbapenems were incorporated into MDR/XDR-TB regimens in the pre-bedaquiline era when background agents were failing and included meropenem (1 to 2 g three times daily) and imipenem (500 mg/1 g 4 times a day or 1 g twice daily) for inpatient treatment and ertapenem was given 1 to 1.5 g intramuscularly daily as a step down for outpatient treatment.

Meropenem and amoxicillin/clavulanic acid were used for the first time in MDR-TB patients in Belgium.[72] In a study conducted in the Netherlands, 18 patients with DR-TB were treated with a multi-drug regimen that contained ertapenem. All patients converted their sputum smears and cultures.[94] Fifteen of the 18 participants completed treatment and were reported cured. Ertapenem was reported to be well tolerated with a favourable pharmacokinetic/ pharmacodynamic profile. Ertapenem EBA was investigated in a clinical trial, with ertapenem administered once daily intravenously or intramuscularly in combination with twice daily oral amoxicillin/clavulanic acid.[73] An oral penem, faropenem showed activity in a TB murine model when combined with amoxicillin, clavulanate and probenecid.[74] A further study by Dhar et al. showed that faropenem, could be given without a beta-lactamase inhibitor.[75] However no activity was detected with the faropenem sodium formulation in two EBAs

performed in people with pulmonary TB (South Africa and South East Asia). It is thought that this was due to the very low oral bioavailability of faropenem sodium and levels of exposure and limited time above the MIC for faropenem led to little activity.[76]

The need for thrice daily intravenous treatment or expensive and painful daily intramuscular treatment severely limits carbapenems as a viable therapeutic option in high TB burden low resource settings. Several technical challenges exist determining the activity of these compounds in vitro due to rapid degradation and lack of DST. This would be a limit to the usefulness of these drugs in clinical practice as DST would not be available.[77]

Nevertheless, the discovery that beta-lactams with beta-lactamase inhibitors can be active against TB has led to renewed research in β-lactams for TB, especially oral agents that can overcome the current implementation barriers. Oral penems with a higher oral bioavailability than faropenem like sanfetrinem and tebipenem are now in late-stage clinical research and could renew interest in B-Lactams for TB. Sanfetrinem an oral penem is currently in an early phase 2 EBA in pulmonary TB patients, results are expected in Q4 2025.

TB in intensive care

A recent systematic review on TB in the intensive care unit (ICU) setting reported that the majority of studies were retrospective small single centred studies and included a large heterogeneity of TB presentations such as respiratory failure, acute respiratory distress syndrome (ARDS), renal and multi organ failure among others; only a third of cases were started on TB treatment.[78-80] Several studies have demonstrated that mortality of TB on ICU is very high (>50%).[81] Severe extrapulmonary forms such as miliary, disseminated and central nervous system (CNS) or TB meningitis, frequently require hospitalisation and admission to ICU.

Despite being critically ill, individuals often receive treatment with oral TB drugs including administration via a nasogastric tube when mechanically ventilated.[82-87] Critical illness may affect TB drug pharmacokinetics as individuals may suffer from altered absorption, clearance, having a larger distribution volume, hypoalbuminemia, and liver and/or renal impairment.[88] Furthermore, absorption of isoniazid and rifampicin and subsequent bioavailability can be significantly reduced when- crushed and administered together with enteral nutrition via a nasogastric tube due to food effect.[89] Intravenous (IV) drug administration could be an option for the management of TB in ICU settings as they may ensure that target levels are reached rapidly at the site of infection to accelerate reduction in bacillary

loads.[90-92] It can be argued that IV treatment as an adjunct to, or in the place of, oral anti-TB therapy could reduce mortality in ICU individuals with TB. However, both good evidence and guidance on such treatment are not currently available in TB management guidelines.

Aims and outline of this thesis

In this thesis we undertook to study the efficacy and safety of several beta-lactams and their combinations, employing cohort data from Italy and the Netherlands. Furthermore we also aimed to determine treatment and outcome of TB patients admitted to ICU and explore whether the use of IV TB treatment regimens could improve patient survival.

In **chapter 2** we gave a comprehensive review on the advances in new and repurposed tuberculosis drugs, treatment regimens, and host-directed therapies aimed at improving outcomes for people with drug-susceptible and drug-resistant TB.

In **chapter 3** we compared the effectiveness and safety of imipenem/clavulanate- versus meropenem/clavulanate-containing regimens in the treatment of MDR- and XDR-TB in several European countries.

In **chapter 4** we evaluated the effectiveness and safety of meropenem/clavulanate-containing regimens in the treatment of MDR- and XDR-TB.

In **chapter 5** we evaluated the effectiveness and safety of Imipenem-Clavulanate added to an optimized background regimen versus control regimens in the treatment of multidrug-resistant and extensively drug-resistant tuberculosis.

In **chapter 6** we describe a case of renal Fanconi syndrome with meropenem-containing regimen in drug-resistant tuberculosis.

In **chapter 7** we present a systematic review on pulmonary tuberculosis in the intensive care setting, with a focus on the use of severity scores.

In **chapter 8** we report a multicentric international observational study of drug management of tuberculosis in the intensive care setting.

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Chapter 2

Tuberculosis: progress and advances in development of new drugs, treatment regimens, and host-directed therapies

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Summary

Tuberculosis remains the world's leading cause of death from an infectious disease, responsible for an estimated 1,674,000 deaths annually. WHO estimated 600,000 cases of rifampicin-resistant tuberculosis in 2016 of which 490,000 were multi-drug-resistant (MDR), with less than 50% survival after receiving recommended treatment regimens. Concerted efforts of stakeholders, advocates, and researchers are advancing further development of shorter course, more effective, safer, and better tolerated treatment regimens. We review the developmental pipeline and landscape of new and repurposed tuberculosis drugs, treatment regimens, and host-directed therapies (HDTs) for drug-sensitive and drug-resistant tuberculosis. 14 candidate drugs for drug-susceptible, drug-resistant, and latent tuberculosis are in clinical stages of drug development; nine are novel in phase 1 and 2 trials, and three new drugs are in advanced stages of development for MDR tuberculosis. Specific updates are provided on clinical trials of bedaquiline, delamanid, pretomanid, and other licensed or repurposed drugs that are undergoing investigation, including trials aimed at shortening duration of tuberculosis treatment, improving treatment outcomes and patient adherence, and reducing toxic effects. Ongoing clinical trials for shortening tuberculosis treatment duration, improving treatment outcomes in MDR tuberculosis, and preventing disease in people with latent tuberculosis infection are reviewed. A range of HDTs and immune-based treatments are under investigation as adjunctive therapy for shortening duration of therapy, preventing permanent lung injury, and improving treatment outcomes of MDR tuberculosis. We discuss the HDT development pipeline, ongoing clinical trials, and translational research efforts for adjunct tuberculosis treatment.

Key messages

- Tuberculosis caused 1.67 million deaths in 2016. Drug-resistant tuberculosis is a now a major threat to global health security.
- WHO recommended treatments can only cure 50% of multidrug-resistant (MDR) tuberculosis and 30% of patients with extensively drug-resistant tuberculosis. Newer, more potent drugs are required that could build a universal regimen for effectively treating and reducing the duration of drug-resistant and drug-sensitive tuberculosis.
- Concerted efforts of stakeholders, advocates, and researchers are slowly advancing the development of shorter course, more effective, safer, and better tolerated treatment regimens.
- 14 candidate drugs for drug-susceptible, drug-resistant, and latent tuberculosis are in the clinical stages of drug development.
- The new diarylquinoline (bedaquiline) and nitroimidazoles (pretomanid, delamanid) provide hope for an all-oral regimen for MDR tuberculosis.
- A range of host-directed therapies (HDTs) are being developed as adjuncts to drug treatment to hasten elimination of *Mycobacterium tuberculosis* infection, shorten the duration of treatment, reduce excessive inflammation, minimise permanent lung damage, and prevent new drug resistance.
- Access to the new drugs and conduct of clinical trials are hampered by high costs. Development of new medicines and regimens should be twinned with funder investments to ensure that these medicines are affordable, effective, safe, and reach the people who need them.
- A substantial increase in political and funder attention is required to increase the inadequate funding portfolio for new drugs and HDTs.

Introduction

In 2016, there were an estimated 10.4 million cases of tuberculosis with 1.67 million deaths, making tuberculosis the ninth leading cause of death worldwide.[1] The 2017 WHO Global Tuberculosis Report estimated 490,000 cases of multidrug-resistant (MDR) tuberculosis, with less than 50% survival in patients who received recommended WHO treatment regimens.[1–6] The Report reveals the dire need for new therapies and approaches for improving tuberculosis treatment delivery and management outcomes. Many challenges remain in developing optimal tuberculosis treatment regimens.[7] Concerted efforts of stakeholders, advocates, and researchers are advancing the further development of shorter course, more effective, safer, and better tolerated treatment regimens. Only three novel drugs are in advanced stages of development for MDR tuberculosis, and nine are being assessed in phase 1 and 2 trials. In addition to new drugs, an array of immune-based treatments and host-directed therapies are under development aimed at eliminating *Mycobacterium tuberculosis* infection, shortening the duration of treatment, preventing permanent lung injury, and preventing development of new drug resistance. This Series paper provides updates on advances and progress in the development pipeline of new and repurposed tuberculosis drugs and host-directed therapies, addressing the unmet needs of treatment management for patients with tuberculosis (Panel 2.1). In this Series paper we

review ongoing clinical trials for shortening tuberculosis treatment, improving treatment outcomes in MDR tuberculosis, and preventing disease in people with latent tuberculosis infection. We also discuss specific issues regarding safety and toxicity, and drug–drug interactions.[9–14] The organisations TB Alliance and WHO Stop TB Partnership provide more information about research and treatment of tuberculosis around the world.

Panel 2.1: Unmet needs of tuberculosis treatment[8]

- A potent and cheap pan-tuberculosis treatment regimen that is well tolerated and can treat both drug-susceptible and drug-resistant disease without cumulative toxic drug effects or increased relapse rates
- Treatment regimens that can improve survival rates in patients with drug-resistant tuberculosis and with *Mycobacterium tuberculosis*–HIV coinfection
- A treatment regimen that is of short duration with minimal side-effects and low pill burden to improve patient acceptance and adherence, and reduce loss to follow-up and treatment failure
- Nearly 50% of patients treated for pulmonary tuberculosis develop long-term lung damage and functional disability (chronic cough, breathlessness, impaired lung function, and reduced longevity, despite treatment success); new strategies are required to prevent, manage, and perhaps reverse the loss in lung function
- Improved treatments for latent *M tuberculosis* infections due to drug-resistant strains
- Adjunct host-directed therapies with tuberculosis drug treatment to minimise or prevent lung injury and long-term functional impairment
- Improved biomarkers to predict response to treatment, risk of relapse, assure cure, and accelerate drug development
- Better supply chain and delivery of drugs to the patients that need them – as of 2017, very few patients with drug-resistant tuberculosis have access to effective treatment
- Increased funder investments into development and assessment of new drugs, host-directed therapies, and biomarkers

Progress in the development of new drugs and treatment regimens

In the past 5 years, development of several new and repurposed antituberculosis drugs has accelerated with the approval of the first new antituberculosis drug in 35 years.[13–17] The advent of diarylquinoline and the nitroimidazoles provides hope for an oral pan-tuberculosis regimen, based on potent specific drugs for which resistance is weak or non-existent. The line-up of the tuberculosis drug development pipeline, as of December, 2017, is shown in Figure 2.1. The class of drugs, their mechanisms of action, trial phase, and relevant sponsors are presented in Table 2.1.[18] PBTZ169 is now in phase 2 early bactericidal activity trials. A new compound, Q203, was assessed in a phase 1 trial completed in 2017, and TBA7371 entered a phase 1 trial in 2017. SQ109 appears to be sterilising in vitro but should not be used with rifampicin, which substantially reduces its levels. Interim results from a double-blind placebocontrolled trial in Russia, in patients with MDR tuberculosis, showed that at 24 weeks 80% of patients receiving SQ109 plus optimised background regimen were

sputum negative compared with 61% patients receiving placebo plus regimen (p=0.048).[19] However, with these advances there have also been some setbacks. Sutezolid yielded promising phase 2 trial results, but some stage 1 studies needed to be repeated because of licensing issues. AZD5847 and TBA–354 showed no activity in phase 1 studies and are associated with neurotoxicity.[20]

14 candidate drugs for drug-susceptible, MDR, and latent tuberculosis are in the clinical stages of drug development; nine are novel, and three have been approved (online).

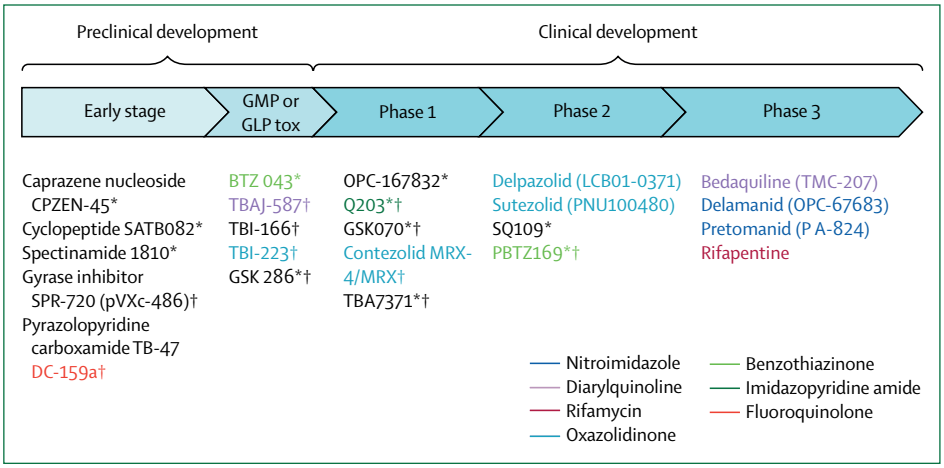


Figure 2.1: Global New TB Drug development pipeline.
Adapted from Stop TB Partnership's Working Group on New TB Drugs (October, 2017) with permission.[17] * New chemical class. † New to phase. GMP: good manufacturing practice; GLP tox: good laboratory practice toxicology studies.

Drug-susceptible tuberculosis

Treatments for patients with drug-susceptible tuberculosis last at least 6 months, requiring the patient to take on average ten pills a day during the intensive phase. WHO recommends treatment for drug-susceptible tuberculosis with an initial 2-month intensive phase (isoniazid, rifampicin, pyrazinamide, and ethambutol daily), continued by dual therapy isoniazid and rifampicin for the last 4 months. The whole course of treatment for the disease is around US$20, and treatment success in programmatic conditions is approximately 85%. Apart from the efficacy and economic value, the regimen is lengthy, hepatotoxic, and not well tolerated by a substantial proportion of patients prescribed the medication. 4-month standard regimens are, so far, only recommended by the American Thoracic Society for patients who are sputum smear and culture negative with minimal pulmonary disease.[11]

Table 2.1: TB Drugs development pipeline

Drug	Target	Sponsors	Phase	Notes
Diarylquinoline				
Bedaquiline	ATP synthase	Janssen, TB Alliance, NIAID, AMRC, the Union, Unitaid, USAID	III	Conditional marketing approval
Nitroimidazole				
Delamanid	Inhibit cell wall synthese and cell respiration	Otsuka, NIAID, Unitaid	III	Conditional marketing approval
Pretomanid	Inhibit cell wall synthese and cell respiration	TB Alliance	III	Potent bactericidal and sterilising activity in mouse models
Oxazolidinone				
Sutezolid	Protein synthesis 23s ribosome	Sequella, NIAID, Medicines Patent pool, TB alliance	IIa	Early bactericidal activity significant reduction in counts of colony-forming units in EBA study.
Delpazolid LCB01-0371	Protein synthesis 23s ribosome	LegoChem Biosciences	II	A phase II safety and early bactericidal activity study of the drug is expected to be completed in late 2017.
Contezolid	Protein synthesis (23s ribosome)	MicuRX Pharmaceuticals	I	Potentially less toxic than linezolid.
1,2-ethylene diamine				
SQ109	Inhibit cell wall synthesis MmpL3	Infectex, Sequella, PanACEA	II/III	May be synergic with bedaquiline. Two SQ109-containing arms in a PanACEA trial testing high-dose rifampin were stopped early because pre-specified efficacy thresholds were not met.[27]

DprE1 inhibitor				
PBTZ169	Inhibit cell wall synthesis	Nearmedic, iM4TB, BMGF	II	Synergies with bedaquiline and clofazimine
OPC-167832	Inhibit cell wall synthesis	Otsuka, BMGF	I	Codeveloped with delamanid
TBA7371	Inhibit cell wall synthesis	Eli Lilly, Foundation for Neglected Disease Research	I	
BTZ 043	Cell wall synthesis	University of Munich, PanACEA	I	Benzothiazinone, synergy with rifampicin, low toxicity, no hepatic enzyme interactions
Imidazopyridine				
Q203	Cytochrome bc complex	Qurient, Infectex, PanACEA	I	A phase I dose-escalation study is under way and an EBA study is expected to start before the end of 2017.[28]
Riminophenazine				
TBI-166	Outer membrane, bacterial respiratory chain and ion transporters	Institute of Materia Medica, TB Alliance	I	
Oxaborole				
GSK 070, GSK 3036656	Protein synthesis Leucyl-tRNA Synthetase	GlaxoSmithKline	I	

Adapted from Treatment Action Group report.[20] NIAID: National Institute of Allergy and Infectious Diseases (USA); SAMRC: South Africa Medical Research Council; The Union: International Union Against Tuberculosis and Lung Disease; USAID: US Agency for International Development; EBA: early bactericidal activity; PanACEA: Pan African Consortium for the Evaluation of Antituberculosis Antibiotics; iM4TB: Innovative Medicines for Tuberculosis Foundation; BMGF: Bill & Melinda Gates Foundation.

Table 2.2: Ongoing TB treatment trials

	Phase	Study population	Study groups	Note
NC-006 STAND (NCT02342886)	3	271 (of original target of 1,200), HIV- and HIV+ adults (aged ≥18 years)	4 months pretomanid (100 mg twice daily or 200 mg once daily), moxifloxacin, pyrazinamide daily, or 6 months pretomanid (100 mg twice daily), moxifloxacin, pyrazinamide daily, or 6 months pretomanid (200 mg once daily), moxifloxacin, pyrazinamide daily vs standard 6 month therapy	Opened February 2015 (paused October 2016–May 2017); accrual not resumed, results March 2018; TB Alliance
APT (NCT02256696)	2	183, HIV- adults (aged ≥18 years)	2 months pretomanid, rifabutin, isoniazid, pyrazinamide daily, and 1 month pretomanid, rifabutin, isoniazid daily, or 2 months pretomanid, rifampicin, isoniazid, pyrazinamide daily, and 1 month pretomanid, rifampicin, isoniazid daily vs 2 months isoniazid, rifampicin, pyrazinamide, ethambutol daily, and 1 month isoniazid, rifampicin daily	Opened April, 2015 (paused October, 2016–May, 2017), results 2019; John Hopkins University, University of Cape Town Lung Institute
TBTC 31/A5349 (NCT02410772)	3	2,500, HIV- and HIV+ adults and children (aged ≥13 years)	2 months isoniazid, rifapentine (1,200 mg), pyrazinamide, and ethambutol daily, and 2 months isoniazid and rifapentine (1,200 mg) daily, or 2 months isoniazid, rifapentine (1,200 mg), pyrazinamide, and moxifloxacin daily, and 2 months isoniazid, rifapentine (1,200 mg), and moxifloxacin daily vs standard 6 month therapy	Opened January, 2016; accrual to close at the end of 2018, results 2020; substudies include interactions of rifapentine and efavirenz, intensive pharmacokinetics and pharmacodynamics of rifapentine, and sputum biomarkers to predict outcomes; CDC TBTC, ACTG
SHINE (ISRCTN63579542)	3	1,200, HIV- and HIV+ children (aged	2 months isoniazid, rifampicin (600 mg), pyrazinamide, and (in some) ethambutol daily, and 2 months isoniazid and rifampicin (600 mg) daily vs standard 6 month therapy	Opened third quarter of 2016, results 2020; treatment shortening strategy trial for children with minimal tuberculosis; India, Uganda, South Africa, and Zambia; BMRC

RIFASHORT (NCT02581527)	3	800, HIV- adults (aged ≥18 years)	2 months isoniazid, rifampicin (1,200 or 1,800 mg), pyrazinamide, and ethambutol daily, and 2 months isoniazid and rifampicin (1,200 or 1,800 mg) daily vs standard 6 month therapy	Opened February, 2017, results January, 2020; St George's London, INTERTB
TRUNCATE-TB	2/3	900, HIV- and HIV+ adults (aged ≥18 years)	2 months various new regimens vs standard 6 month therapy	Opened late 2017, results 2021; MAMS adaptive trial design; Thailand, Indonesia, Philippines, and Singapore; BMRC, NUS
HIGHRIF 1 Extension (NCT01392911)	2	30, HIV- adults (aged ≥18 years)	EBA safety, tolerability, pharmacokinetics study: 14 days rifampicin 50 mg/kg (3,000 mg) daily	Opened September, 2017, results mid-2018; PanACEA
STEP	2c	600, HIV- adults (aged ≥18 years)	3–4 months isoniazid, rifampicin (600 mg), pyrazinamide, and Q203 daily, or 2–3 months isoniazid, rifampicin (high dose), pyrazinamide (high dose), and Q203 daily vs standard 6 month therapy	Opens mid-2018, results 2021; adaptive trial design, examining new treatment backbones; PanACEA
NC-008 SimpliciTB (NCT03338621)	2c/3	300, HIV- and HIV+ adults (aged ≥18 years)	4 months bedaquiline, pretomanid, moxifloxacin, pyrazinamide vs standard 6 month therapy	Opens August, 2018, results 2022; TB Alliance

Standard 6 month therapy is 2 months isoniazid, rifampicin (600 mg for patients ≥50 kg and 450 mg for patients <50 kg), pyrazinamide, ethambutol daily, and 4 months isoniazid and rifampicin (600 mg for patients ≥50 kg and 450 mg for patients <50 kg) daily. CDC TBTC: Centers for Disease Control and Prevention Tuberculosis Trials Consortium; ACTG: AIDS Clinical Trials Group; MAMS: multiarm multistage trial; BMRC: British Medical Research Council; NUS: National University of Singapore; EBA: early bactericidal activity; PanACEA: Pan African Consortium for the Evaluation of Antituberculosis Antibiotics.

Table 2.2 summarises the ongoing drug trials aimed at shortening and simplifying regimens for drugsusceptible tuberculosis and improving management, including increasing patient adherence.

Studies investigating the optimisation of the use of approved drugs with improved formulations and pill counts are also ongoing.[21] More palatable fixed-dose combination tablets are now available for paediatric use, simplifying dosing in children weighing less than 25 kg,[22] while improving drug delivery and drug adherence.[23,24] Efforts are also being made to render the standard quadruple regimens less toxic. One study[25] showed that liver toxicity was reduced when methionine and vitamin B complex were added to the standard regimen.

Research on rifampicin, which was introduced in the 1970s, is centred on determining the therapeutic window and assessing higher doses, which can achieve greater potency than lower doses. A phase 2 trial[26] showed that 20 mg/kg of rifampicin did not increase efficacy when compared with 10 mg/kg of rifampicin and 15 mg/kg of rifampicin together with isoniazid, ethambutol, and pyrazinamide. The PanACEA trial (NCT01785186),[27] the first multiarm multistage (MAMS) study of tuberculosis treatment, investigated 20 mg/kg and 35 mg/kg doses of rifampicin against a standard 10 mg/kg dose in patients with drug-susceptible tuberculosis. The 35 mg/kg dose was safe and the 35 mg/kg group had faster 8-week culture conversion times than both the 20 and 10 mg/kg groups, which might lead to shorter treatment durations. The addition of SQ109 or moxifloxacin did not achieve superiority over the standard quadruple regimen.

The RIFASHORT (NCT02581527) and NC-006 STAND (NCT02342886) trials are focused on shortening the standard tuberculosis regimen, assessing the efficacy of high-dose rifampicin and an entirely new regimen. Rifapentine is being tested at a flat dose of 1,200 mg daily in the Tuberculosis Trials Consortium (TBTC) Study 31/A5349; the phase 3 study will recruit 2,500 patients without HIV and those living with HIV with CD4 count above 100 cells per µL. The first experimental group includes rifapentine and isoniazid for 4 months, with ethambutol and isoniazid for the first 2 months. The second experimental group replaces ethambutol with 4 months of moxifloxacin. The control group is the standard 6-month therapy.

The TRUNCATE-TB[28] is a phase 2c open-label MAMS trial assessing the treatment of drug-susceptible tuberculosis in just 2 months, administering high-dose rifampicin, bedaquiline, delamanid, and linezolid in different combinations over five experimental groups. Treatment is extended to 12 weeks if study participants are still symptomatic or smear positive at week 8. Moxifloxacin is often used as a substitute for isoniazid or ethambutol in patients

with monoresistant tuberculosis, or in patients with intolerability or contraindications (or both); however, moxifloxacin did not show potency in shortening regimens. Concomitant rifampicin reduces concentration of moxifloxacin in the blood by up to 31%, so higher doses of moxifloxacin might be required.[29] Concerns over QT prolongation have led to new studies to investigate the phenomenon. 1,602 patients from the OFLOTUB cohort (NCT00216385)[30] who had received quinolone-containing regimens contributed to the analysis of Fridericia's formula (QTcF) by treatment group in an extensive survey of QT prolongation. Neither a standard 6-month nor a 4-month gatifloxacin-based regimen seemed to carry a sizeable risk of QT prolongation in patients with newly diagnosed pulmonary tuberculosis. Gatifloxacin, a component of the Bangladesh regimen, is no longer on the WHO essential drug list due to concerns over dysglycaemia, and it has been replaced in the shorter drug regimen by moxifloxacin, a drug which is known to prolong QTc.[30]

Drug-resistant tuberculosis

The taxonomy of antituberculosis drugs and their combinations is undergoing a rapid transformation as a result of new clinical trials data and meta-analyses.[31,32] The updated classification of new antituberculosis drugs by WHO (Panel 2.2) guides physicians in constructing an effective drug-resistant treatment regimen that is patient specific, based on a minimum of four active drugs.[33] The regimen recommends two core drugs (a later-generation fluoroquinolone and an injectable aminoglycoside), and then the addition of other core drugs (e.g., ethionamide or prothionamide, cycloserine or terizidone, linezolid, and clofazimine); if further drugs are required because of resistance or intolerance, then non-core drugs such as bedaquiline (especially if the patient is quinolone resistant) or delamanid should be added (combination of these two drugs is not recommended). Non-core drugs, such as para-aminosalicylic acid, carbapenems with clavulanate are reserved for patients with extensively drug-resistant (XDR) tuberculosis, with few therapeutic options. Pyrazinamide and ethambutol might be added, but they should not be counted as active drugs in the regimen.[33,34] A retrospective study[35] showed that the use of rifabutin was associated with improved treatment outcomes compared with no rifabutin treatment in patients with MDR tuberculosis. At least 20 new drugs are estimated to be required in phase 1 and 2 trials to ensure that a few progress to phase 3 assessment. With research investment being at its lowest amount since 2008, more resources are urgently required.[36]

Table 2.3 summarises the ongoing drug trials aimed at shortening and simplifying regimens for drug-resistant tuberculosis. Three drugs are in phase 3: bedaquiline, delamanid, and

pretomanid, of which delamanid and pretomanid are nitroimidazoles and unlikely to be used together. Nine candidates are in phase 1 and 2 studies; five of the drugs are from two classes (oxazolidinones and DprE1 inhibitors). Sutezolid and delpazolid are two newer generation oxazolidinones in early clinical trials that are anticipated to be just as effective as linezolid, but less toxic.

Panel 2.2: WHO categorisation of second-line antituberculosis drugs recommended for treatment of rifampicin-resistant and multidrug-resistant tuberculosis[33]

Group A: fluoroquinolones
- Levofloxacin
- Moxifloxacin
- Gatifloxacin

Group B: second-line injectable drugs
- Amikacin
- Capreomycin
- Kanamycin
- Streptomycin*

Group C: other core second-line drugs
- Ethionamide or prothionamide
- Cycloserine or terizidone
- Linezolid
- Clofazimine

Group D: add-on drugs (not part of the core multidrug-resistant regimen)

D1
- Pyrazinamide
- Ethambutol
- High-dose isoniazid

D2
- Bedaquiline
- Delamanid

D3
- Para-aminosalicylic acid
- Imipenem plus cilastatin (requires clavulanate)
- Meropenem (requires clavulanate)
- Amoxicillin plus clavulanate
- Thioacetazone†

* Caution: streptomycin is frequently resistant and unlikely to be active against drug-resistant tuberculosis. † Thioacetazone can give serious adverse events. HIV-negative status needed before administering thioacetazone. Not to be administered to people who are HIV-positive.

Table 2.3: Ongoing and planned treatment trials for drug-resistant tuberculosis

	Phase	Study population	Study groups	Notes
Otsuka Trial 213 (NCT01424670)	3	511, HIV- adults (aged ≥18 years)	2 months delamanid (100 mg twice daily) and 4 months delaminid (200 mg daily) plus OBR vs 6 months placebo plus OBR	Opened September 2011, completed June, 2016, preliminary findings presented at IUATLD October, 2017, confirm efficacy with less toxicity, results mid-2018; Otsuka
STREAM Stage 1 (ISRCTN78372190)	3	424, HIV- and HIV+ adults (aged ≥18 years)	4 months daily moxifloxacin, clofazimine, pyrazinamide, ethambutol, isoniazid (high dose), kanamycin (daily for 3 months, then 3 times per week), prothionamide, and 5 months of moxifloxacin, clofazimine, pyrazinamide, ethambutol daily	Opened 2012, closed to accrual June, 2015, preliminary findings presented at IUATLD October, 2017, results mid-2018; IUATLD, BRMC, USAID
NC-005 (NCT02193776)	2b	60, HIV- adults (aged ≥18 years)	Serial sputum culture counts: 8 weeks bedaquiline (200 mg daily), pretomanid (200 mg daily), moxifloxacin, pyrazinamide, single arm study with long follow-up	Opened November, 2014, preliminary findings presented at CROI, 2017, results mid-2018; TB Alliance
OPTI-Q (NCT01918397)	2	100, HIV- and HIV+ adults (aged ≥18 years)	6 months levofloxacin (14, 17, or 20 mg/kg/d) plus OBR vs 6 months levofloxacin (11 mg/kg/d) plus OBR	Opened January, 2015, results mid-2018; South Africa, Peru; NIAID, Boston University, CDC TBTC
NC-006 STAND (NCT02342886)	3	13 (of original target of 300), HIV- and HIV+ children (aged ≥14 years)	6 months pretomanid (200 mg), moxifloxacin, pyrazinamide daily, single arm study	Opened February, 2015, paused October, 2016–May, 2017, accrual not resumed, results March, 2018; TB Alliance
NiX-TB (NCT02333799)	3	109 (of original target of 300), HIV- and HIV+ adults (aged ≥18 years)	6 months bedaquiline (200 mg daily for 2 weeks then 200 mg three times weekly), pretomanid (200 mg daily), linezolid (600 mg twice daily), single arm study	Opened March, 2015, preliminary findings presented at CROI, 2017, accrual closed November, 2017, with opening of NC-007 ZeNiX trial; TB Alliance
NExT-5001 (NCT02454205)	2/3	300, HIV- and HIV+ adults (aged ≥18 years)	6–9 months bedaquiline, linezolid, levofloxacin, pyrazinamide, and either high-dose isoniazid or ethionamide or terizidone daily (all oral) vs 6–8 months kanamycin, moxifloxacin, pyrazinamide, ethionamide, terizidone daily, and 16–18 months moxifloxacin	Opened October, 2015, results January, 2019; University of Cape Town

Table 2.3 continues on next page.

Table 2.3: ***Continued***

	Phase	Study population	Study groups	Notes
MDR-END (NCT02619994)	2	238, HIV- and HIV+ adults (aged ≥18 years)	9 or 12 months delamanid, levofloxacin (750 or 1,000 mg), linezolid (600 mg daily for 2 months, 300 mg daily thereafter) vs local regimen	Opened January, 2016, results December, 2019; Korea
STREAM Stage 2 (NCT02409290)	3	1,155, HIV- and HIV+ adults (aged ≥18 years)	9 months moxifloxacin, clofazimine, ethambutol, pyrazinamide daily, with initial 2 months isoniazid, kanamycin, prothionamide daily, or 9 months bedaquiline, clofazimine, ethambutol, levofloxacin, pyrazinamide daily, with initial 2 months isoniazid (high dose), prothionamide daily (all oral), or 6 months bedaquiline, clofazimine, levofloxacin, pyrazinamide daily, with initial 2 months isoniazid (high dose) and kanamycin vs 20–24-month local regimen	Opened April, 2016, results April, 2021; IUATLD, BMRC, USAID, TB Alliance
Janssen C211 (NCT02354014)	2	60, HIV- adults (aged ≥18 years)	Pharmacokinetics, safety, dose-range 6 months bedaquiline (daily for 2 weeks, then 3 times a week) plus OBR, single arm study	Opened May, 2016, results March 2021; India, Philippines, Russia, South Africa; Janssen
ACTG A5343 DELIBERATE (NCT02583048)	2	84, HIV- and HIV+ adults (aged ≥18 years)	Pharmacokinetics, QTC 6 months bedaquiline daily plus OBR, or 6 months delamanid daily plus OBR, or 6 months bedaquiline and delamanid daily plus OBR	Opened August, 2016, results 2019; ACTG
endTB (NCT02754765)	3	750, HIV- and HIV+ adults (aged ≥18 years)	9 months bedaquiline, linezolid, moxifloxacin, pyrazinamide daily, or 9 months of bedaquiline, linezolid, clofazimine, levofloxacin, pyrazinamide daily, or 9 months of bedaquiline, linezolid, delamanid, levofloxacin, pyrazinamide daily, or 9 months of delamanid, linezolid, clofazimine, levofloxacin, pyrazinamide daily, or 9 months of delamanid, clofazimine, moxifloxacin, pyrazinamide daily vs local regimen	Opened December, 2016, results September, 2020; Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru; MSF, Partners in Health

TB-PRACTECAL (NCT02589782)	2/3	630, HIV- and HIV+ adults (aged ≥18 years)	6 months bedaquiline, pretomanid, moxifloxacin, linezolid daily, or 6 months bedaquiline, pretomanid, linezolid, clofazimine daily, or 6 months bedaquiline, pretomanid, linezolid daily (all oral) vs local regimen	Opened January, 2017, results March, 2021; Belarus, South Africa, Uzbekistan; MSF
IMPAACT P1108 (NCT03141060)	2	72, HIV- and HIV+ children (aged	Pharmacokinetics, safety, dose-range 6 months bedaquiline (daily for 2 weeks, then 3 times a week) plus OBR, single arm study	Opened June, 2017, results June, 2020; Haiti, India, South Africa; IMPAACT
NC-007 ZeNiX (NCT03086486)	3	180, HIV- and HIV+ adults and children (aged ≥14 years)	2 or 6 months linezolid (600 or 1,200 mg daily, double-blinded), bedaquiline (200 mg daily for 2 weeks, then 100 mg daily), and pretomanid (200 mg daily)	Opened November, 2017, results January, 2021
IMPAACT 2005 (NCT03141060)	1/2	48, HIV- and HIV+ children (aged	Pharmacokinetics, safety 6 months delamanid (100 mg twice daily) plus OBR, single arm study	Opened January, 2018, results April, 2021; Botswana, India, South Africa, Tanzania; IMPAACT
ACTG A5356	2a	240, HIV- and HIV+ adults (aged ≥18 years)	6 months delamanid (100 mg twice daily), linezolid (300 or 600 mg daily or 1,200 mg every other day) plus OBR (oral) vs 6 months delamanid (100 mg twice daily) plus OBR (injectable)	Opens August, 2018; ACTG
NC-008 SimpliciTB (NCT03338621)	3	150, HIV- and HIV+ adults (aged ≥18 years)	6 months bedaquiline, pretomanid, moxifloxacin, pyrazinamide daily, single arm study	Opens August, 2018, results March 2022; TB Alliance

OBR: optimised background regimen; IUATLD: International Union against Tuberculosis and Lung Disease; BMRC: British Medical Research Council; USAID: United States Agency for International Development; CROI: Conference on Retroviruses and Opportunistic Infections; MSF: Médecins sans Frontières; NIAID: National Institute of Allergy and Infectious Diseases (US National Institutes of Health); CDC TBTC: Centers for Disease Control and Prevention Tuberculosis Trials Consortium; ACTG: AIDS Clinical Trials Group; IMPAACT: International Maternal Pediatric Adolescent AIDS Clinical Trials Network.

Bedaquiline

Bedaquiline (a diarylquinoline inhibiting ATP synthase), delamanid, and pretomanid are being investigated in some novel trials that are assessing their use as single drugs and in combination. By October, 2017, an estimated 12,194 patients had received bedaquiline.[37] The WHO caution on the potential toxic effects of bedaquiline originated from the observation of ten unexpected late deaths in the bedaquiline group of the C208 phase 2b trial.[38] A systematic review[39] of published results from 1,293 patients treated with bedaquiline reported that QT was greater than 450 ms for 35 (11%) of 329 people, and greater than 500 ms for 42 (3%) of 1,293 people. In 44 (3%) of 1,293 people, bedaquiline was stopped because of adverse events. In eight (1%) of 857 people, bedaquiline was discontinued specifically because of QT prolongation. Of these eight participants, two were restarted on bedaquiline after temporary interruption. A retrospective study[40] of 428 patients with MDR tuberculosis, treated under programmatic conditions with bedaquiline, from across 15 countries, suggested that the risk of QT prolongation appears to be less than was initially envisaged. At the end of treatment, sputum smear conversion was observed in 126 (90%) of 140 patients and culture conversion in 191 (92%) of 208 patients. 25 (6%) of 428 patients discontinued the drug because of adverse events, with one death related to non-bedaquiline-related arrhythmia. Importantly, a significant clinical interaction appears to occur between rifamycins and bedaquiline, leading to a reduction in concentration of bedaquiline in the blood. As a result, the combined use of these two drugs are restricted in their use to treat drug-sensitive tuberculosis.

Delamanid

By October, 2017, 976 patients had received delamanid, made available by Otsuka, for a compassionate use programme that used approval processes of the European Respiratory Society–WHO Tuberculosis Consilium, Médecins Sans Frontières (MSF), and others.[37,41,42] The Otsuka proprietary delamanid studies yielded consistent favourable outcomes (e.g., sputum smear and conversion): phase 2 trial 204, 143 (74%) of 192 people;[43] phase 3 trial 213, 276 (81%) of 339 people;[44] and programmatic use in Latvia, 17 (84%) of 19 people.[45] Results of these compassionate use programmes are encouraging, with 53 (80%) of 66 patients achieving sputum culture conversion.[46] The efficacy and safety of the use of delamanid in children older than 6 years is under investigation through several studies: the Otsuka Trial 233 (NCT01859923) is a 6-month pharmacokinetic and safety study in all paediatric weight groups, and results are expected in 2020; results of the Otsuka Trial 232, (NCT01856634) with 18-day pharmacokinetic and safety in different groups aged 0–17 years, are due out in 2018.[42,47,48]

Results of the first phase 3 trial studying the use of delamanid for treatment of MDR tuberculosis (Otsuka Trial 213, NCT01424670) were presented at the 48th Union World Conference on Lung Health in October, 2017 (Guadalajara, Mexico). The primary endpoint was time to sputum culture conversion over the first 6 months of delamanid plus optimised background regimen versus placebo and optimised background regimen. Patients in the delamanid group had a more rapid culture conversion of 6–13 days than the placebo group, with a nonsignificant p-value for efficacy of 0.056. The proportions of patients who had favourable treatment outcomes at 24 months were similar in both groups. Importantly, adverse events did not increase significantly in the delamanid group. Moreover, delamanid reduced the development of fluoroquinolone resistance (NCT01424670). Despite the disappointing results, delamanid is a specific antituberculosis medication with an excellent safety profile, making it a useful companion drug in a regimen and useful for reducing the development of resistance. Delamanid has few drug–drug interactions and might be useful in patients who are co-infected with HIV, and who have a higher risk of being unresponsive to treatment than those with tuberculosis alone.

Reports indicate[49,50] that treatment with delamanid and bedaquiline in combination might well be tolerated. Although WHO does not recommend this combination because of concerns that bedaquiline and delamanid, which both prolong QT, would have potential detrimental effects in patients, it recognises that physicians might require guidance and has provided recommendations, including active safety drug monitoring, which itself might assist more rapid phase 4 safety data collection. Two trials (NCT02583048, NCT02754765) will study the coadministration of these two drugs. The AIDS Clinical Trials Group study[51] A5343 DELIBERATE includes three groups – delamanid, bedaquiline, and a combination of the two in a shorter regimen of 24 weeks – and seeks to understand whether the combination is safe and to compare the mean changes from baseline (averaged over 8–24 weeks) in QTcF when delamanid and bedaquiline are given in combination to the mean change seen when each drug is given alone.

Pretomanid

Pretomanid, a nitroimidazole developed by the TB Alliance, is being considered as a potential component for a pan-tuberculosis regimen for both drug-susceptible and MDR tuberculosis. The drug is being assessed in several trials for drug-susceptible and drug-resistant tuberculosis (NC-005, NC-006 STAND, NiX-TB, TB-PRACTECAL, NC007 ZeNiX, NC-008 SimpliciTB). Of particular note, the NC-005 trial (NCT01498419) is studying a combination of bedaquiline, pretomanid, and pyrazinamide for 8 weeks in patients with drug-susceptible tuberculosis,

with a separate group for patients with drug-resistant tuberculosis with the addition of moxifloxacin to the regimen. The bedaquiline, pretomanid, and pyrazinamide combination had greater antimycobactericidal activity than the standard quadruple regimen.[52] This combination was exquisitely bactericidal: sputum was converted in 78–96% of patients receiving bedaquiline, pretomanid, and pyrazinamide with moxifloxacin at 8 weeks of treatment, depending on whether the *M tuberculosis* strain was susceptible to the drugs in the regimen. Clearance was also up to three-times faster than the comparison group on standard quadruple therapy.[52] Regimens with bedaquiline, pretomanid, and pyrazinamide, along with moxifloxacin, reduce pill burden and might be potent enough to reduce treatment duration to 3 months in total. The regimen of bedaquiline, pretomanid, and pyrazinamide with moxifloxacin could be advantageous for patients with MDR tuberculosis by offering a shorter injectable-free regimen that might be able to treat the majority of patients. The NC-008 SimpliciTB study (NCT03338621) will investigate a 4-month regimen of bedaquiline, pretomanid, and pyrazinamide with moxifloxacin in patients with drugsusceptible tuberculosis versus standard isoniazid, rifampicin, pyrazinamide, and ethambutol plus this combination for 6 months in patients with MDR tuberculosis.

Repurposed drugs

The antileprosy drug clofazimine has shown sterilising and treatment-shortening potential. A new rimino-phenazine, TBI-166, has entered phase 1 trials (Table 2.1) and will hopefully not produce skin discolouration, a common side effect of clofazimine.[53] A sizeable programmatic study in Brazil used clofazimine in a standardised 2006 MDR tuberculosis regimen, replacing pyrazinamide. 1,446 patients were treated with clofazimine-containing regimens and 1,096 with pyrazinamide-containing regimens. The clofazimine-containing regimen was found to have similar success to the pyrazinamide-containing regimen, but more patients in the clofazimine group responded to treatment and fewer were lost to follow-up.[54] Bedaquiline and clofazimine have been shown to have cross-resistance with the mutation in Rv0678, leading to increased removal of these drugs by the MmpL5 efflux pump.[55]

Meta-analyses and systematic reviews of the use of carbapenems (ertapenem, imipenem, meropenem) for treatment of MDR and XDR tuberculosis on the basis of clinical necessity indicate a role for their use in tuberculosis treatment.[56–58] They appear very active with excellent tolerability and safety records. However, the absence of an active oral formulation and the need for the combination of amoxicillin plus clavulanic acid (which protects meropenem or carbapenem from β-lactamases) reduce the appeal of carbapenems. Faropenem (an oral penem) showed little activity in a phase 2b trial[58] despite promising

hollow fibre studies.[58–60] This result might be due to the low oral bioavailability of faropenem sodium.[61] Future development of oral penem or carbapenem formulations could offer another solution to the need for a pan-tuberculosis regimen.[62,63] Similarly, another β-lactam, ceftazidime, combined with the new β-lactamase inhibitor avibactam, has shown encouraging preclinical results. The *M tuberculosis* class A β-lactamase is potently inhibited by avibactam, rendering ceftazidime active against mycobacteria.[64]

Linezolid, an oxazolidinone, has shown antimycobacterial efficacy and is included in many drug trial regimens.[65] Its toxicity profile has restricted its use beyond drug-resistant tuberculosis. In vitro model dose-ranging studies have identified optimal linezolid doses for use in combination therapy, maximising bactericidal activity, while avoiding toxic effects. Ongoing pharmacokinetic and pharmacodynamic studies[66–68] are clarifying many dosing issues associated with new or repurposed drugs.

Newer regimens for drug-resistant tuberculosis

Injectable-free regimens

Newer treatment regimens for MDR tuberculosis are focused on assessment of injectable-free regimens to reduce the substantial toxic effects (ototoxicity and nephrotoxicity), simplify the logistics of administration of injectable drugs, and improve patient adherence. The NeXT trial (NCT02454205) compares a new, all oral 6–9-month regimen of bedaquiline, linezolid, levofloxacin, and pyrazinamide, with either high-dose isoniazid or ethionamide or terizidone daily, with the standard WHO treatment regimen of 21–24 months, in patients with MDR tuberculosis.

Shorter treatment regimens

A standardised Bangladesh regimen (high-dose gatifloxacin, clofazimine, ethambutol, and pyrazinamide supplemented by prothionamide, kanamycin, and doubledose isoniazid during the 4-month intensive phase) cured 181 (87.9%, 95% CI 82.7–91.6) of 206 people, with no relapses.[69] A further study[70] reported a bacteriologically favourable outcome in 435 (84%) of 515 people. WHO, in 2016, subsequently recommended a shorter, standardised 9–12-month regimen for people with pulmonary MDR or rifampicin-resistant tuberculosis susceptible to aminoglycosides and fluoroquinolones. Exclusion criteria include pregnancy, extrapulmonary cases, and patients who underwent previous treatment with second-line drugs.[33] The 4–6-month intensive phase includes moxifloxacin, an injectable (amikacin or kanamycin), ethionamide or prothionamide, clofazimine, high-dose isoniazid (10 mg/

kg to a maximum of 600 mg a day), ethambutol, and pyrazinamide, and the 5-month continuation phase includes moxifloxacin, clofazimine, ethambutol, and pyrazinamide.[70,71] The only difference between the Bangladesh regimen and the WHO shorter regimen is the substitution of gatifloxacin for moxifloxacin. A meta-analysis2 reported the effectiveness of this regimen for treating MDR tuberculosis, although quinolone resistance was associated with unsuccessful treatment and relapse (odds ratio 46, 95% CI 8–273). Several research centres have attempted to foresee what effect the shorter regimen would have in their setting – a subject that is much debated.[72–75]

The phase 3 STREAM Stage 1 trial76 assessed the 2011 WHO standard MDR tuberculosis regimen (20–24 months), and compared it with the current WHO MDR tuberculosis regimen (9 months). Although interim results suggest the more recent regimen is not non-inferior, it might be a good option for selected patients because treatment success was achieved in 78.1% of participants with the regimen compared with 80.6% in the individualised 20–24-month regimen. Severe adverse events were similar in both groups, although a higher frequency of cardiac conduction disorders was observed in patients who received the shorter 9-month regimen.[76] A phase 3 STREAM Stage 2 trial (NCT02409290) is establishing whether bedaquiline could play a part in a shorter regimen, by comparing 6-month and 9-month all-oral bedaquiline-containing regimens against the locally used WHO-approved MDR tuberculosis regimen, and the 18-month WHO MDR tuberculosis regimen – results are expected in 2021.

The NiX-TB trial (NCT02333799) assessed a 6-month regimen of bedaquiline, pretomanid, and linezolid (600 mg twice daily). For situations in which a patient does not culture convert by month 4, the regimen is prolonged to 9 months. As of October, 2017, 109 participants were enrolled in the study, 70 of whom had completed the 6-month treatment course, with 31 reaching 6-month follow-up. The proportion of patients who have achieved a relapse-free cure to date was 26 (87%) of 30 participants, whereas early mortality was reported in four participants in the first 2 months. 65% people achieved culture conversion by week 8 and 100% by week 16.[77] In November, 2017, NiX-TB rolled over into the new NC-007 ZeNiX trial (NCT0258972), which includes a dose-ranging study for linezolid. The TB-PRACTECAL (NCT02589782) is an adaptive-design study assessing culture conversion at week 8, outcome, and safety of a short regimen (6 months) versus the WHO-recommended MDR tuberculosis regimen (locally used and accepted), including bedaquiline, pretomanid, and linezolid, with or without moxifloxacin or clofazimine, to treat adults with MDR or XDR tuberculosis. The endTB is an MSF and UNITAID study (NCT02754765) that aims to develop one to three priority regimens for the treatment of MDR and XDR tuberculosis and to increase access to bedaquiline and delamanid. The study is a phase 3 trial comparing

five experimental groups with a standard-of-care control, which may include delamanid or bedaquiline. High rates of culture conversion at 6 months and low culture reversion rates at 12 months are preliminary findings.[78]

Updates on tuberculosis drugs for latent infection

Clinicians and patients have long desired shorter, more tolerable, and safer alternatives for treatment of latent tuberculosis infection than standard daily isoniazid for 9 months or more. In 2011, the phase 3 TBTC Study 26 (NCT00164450), undertaken in 7,731 participants, showed non-inferiority of weekly rifapentine and isoniazid (given for 3 months) when compared with 9 months of daily isoniazid.[79] Rifapentine is still unavailable in most countries worldwide. To date, no data are available from phase 3 trials of eradication of latent infection due to drugresistant *M tuberculosis*, though two trials are underway assessing 6 months of daily levofloxacin versus placebo, and a large trial will soon begin assessing 6 months of daily delamanid versus 9 months of daily isoniazid, in adults and children. Drug-resistant latent tuberculosis infection is a high priority for the control of the growing drug-resistant tuberculosis threat.[80]

Table 2.4 summarises ongoing and planned trials investigating chemoprophylaxis for individuals exposed to drug-susceptible and drug-resistant tuberculosis that are underway or will open soon.

Advances and progress in host-directed therapies

Effective host immunity prevents *M tuberculosis* from causing disease in most individuals. Waning host defence leads to increased susceptibility to disease and poor treatment outcomes as illustrated by *M tuberculosis* and HIV co-infection. Augmentation of beneficial immune responses might serve as useful adjunct therapy to tuberculosis drug-treatment regimens.[81] Host-directed therapy (HDT) approaches (Table 2.5) are now a focus for use as adjunct treatment options for MDR tuberculosis, for shortening treatment duration, limiting immunopathology by modulating aberrant *M tuberculosis*-induced immune responses, and improving treatment outcomes.[8,81] Immunotherapy is revolutionising cancer treatment, and similar host pathways operational in tuberculosis are being investigated. Three main approaches are being taken forward for HDT as adjunct therapy for tuberculosis treatment: amplification of host immunity, modulation of inflammation to reduce lung tissue destruction, and killing or containment of *M tuberculosis*.

Table 2.4: Ongoing and planned trials for the treatment of latent tuberculosis infection

	Phase	Study population	Study groups	Notes
Drug-susceptible infection				
A5279 (NCT01404312)	3	3,000, HIV+ adults (aged ≥18 years)	1 month isoniazid (300 mg) and rifapentine (600 mg) daily vs 9 months isoniazid (300 mg) daily	Opened May, 2012, results March, 2018; pharmacokinetic substudy of rifapentine and efavirenz completed; ACTG
CORTIS, CORTIS-HR (NCT02735590)	3	3,200, HIV- adults (aged ≥18 years) and 860 HIV+ adults (aged ≥18 years), stratified by risk of active tuberculosis by transcriptomics	12 doses isoniazid (maximum 900 mg) and rifapentine (900 mg) weekly vs no intervention	Opened July, 2016, results September, 2018; University of Cape Town Lung Institute
WHIP3TB (NCT02980016)	1/2	82, HIV- and HIV+ pregnant or lactating women (aged ≥18 years)	Pharmacokinetics, safety: 12 doses isoniazid (maximum 900 mg) and rifapentine (900 mg) weekly	Opened February, 2017; results December, 2018; IMPAACT
IMPAACT 2001 (NCT02651259)	2	80, HIV- and HIV+ children (aged	Pharmacokinetics, safety: 12 doses weekly rifapentine (25–35 mg/kg) plus isoniazid (10–15 mg/kg) in children aged	Opens March, 2018, results 2021; South Africa; CDC TBTC, Sanof
Drug-resistant infection				
V-QUIN MDR (ACTRN12616000215426)	3	2,006, HIV- and HIV+ adults and children (aged ≥15 years)	6 months levofloxacin (250, 500, or 750 mg) vs placebo (blinded, cluster randomised)	Opened, 2016, results, 2019; Vietnam, Australia; NHMRC
TB-CHAMP (ISRCTN92634082)	3	1,556, HIV- and HIV+ children (aged ≤5 years)	6 months levofloxacin (15–20 mg/kg daily) vs placebo (blinded, cluster randomised)	Opened late 2017, results, 2021; South Africa; BMRC
ACTG A5300B/IMPAACT I2003B PHOENIx	3	3,452, HIV- and HIV+ adults and children (aged ≥6 years)	6 months delamanid (maximum 200 mg once daily) vs 9 months isoniazid (300 mg daily)	Opens mid-2018; ACTG, IMPAACT

CDC TBTC: Centers for Disease Control and Prevention Tuberculosis Trials Consortium; IMPAACT: International Maternal Pediatric Adolescent AIDS Clinical Trials Network; NHMRC: Australia National Health and Medical Research Council; BMRC: British Medical Research Council; ACTG: AIDS Clinical Trials Group.

Small-molecule drugs and enzymes that have therapeutic value in metabolic diseases are being investigated for their usefulness as HDTs. Metformin has been shown to augment immune effector function and reduce *M tuberculosis* burden in preclinical tuberculosis models.[83] Other HDTs being assessed are commonly used over-the-counter drugs that are safe and cheap, such as aspirin, indomethacin, as well as vitamins and biological compounds – e.g., flavonoids and stilbenoids. Therapeutic antibodies targeting cell surface molecules of *M tuberculosis*-infected cells, or molecules that neutralise circulating proteins detrimental to protective immunity, are being developed as HDT options for use as adjuncts with antituberculosis treatment regimens. Exosomes released by T and B lymphocytes might enhance anti-*M tuberculosis* immune reactivity. MHC-peptide complexes, micro RNA, and fragments of DNA, as well as apoptosis inducers such as Fas ligand, could play an overall part in immunomodulation.[84,85] Translational studies incorporating novel technologies, such as tissueembedded microchips and ex-vivo three-dimensional culture models, are underway for studying HDTs[86] (for further preclinical and translational research HDT strategies see online appendix).

Immunotherapeutic targets

Small molecule drugs

Glucocorticoids and receptor agonists, such as dexamethasone and prednisone, have anti-inflammatory properties.[87] Earlier studies[88–90] have shown survival benefits and faster radiological response linked to adjunct corticosteroid treatment in pulmonary tuberculosis, tuberculosis-immune reconstitution inflammatory syndrome, and other forms, including tuberculosis pericarditis, pleurisy, and meningitis. Improved lung pathology and reduced bacillary burden has, however, only been reported for pulmonary tuberculosis during early disease.[91] Biological mechanisms underlying disparate outcomes could be related to glucocorticoid contribution to mycobacterial survival, but this theory requires further investigation.[92] Larger ongoing trials divide further evidence regarding the durable improvement of pulmonary and disseminated tuberculosis, irrespective of HIV, to present a case for glucocorticoids as HDT in tuberculosis (Table 2.5).

Eicosanoids are generated by metabolism of arachidonic acid by cyclooxygenase (COX) to generate prostaglandins, and by lipoxygenase (5-LOX) to generate leukotriene.[93] Selective COX-2 inhibitors decrease unproductive inflammation and improve survival in murine tuberculosis by direct antimycobacterial activity.[94,95] However, COX-2 inhibition is also associated with cell necrosis, which favours in vitro and in vivo *M tuberculosis* survival.[96]

Table 2.5: Host-directed therapies – ongoing clinical trials

Candidate(s)/strategies	Description	Remarks	Trial number
N-acetylcysteine	N-acetylcysteine plus rifampicin, isoniazid, pyrazinamide, and ethambutol to exert simultaneous antituberculosis and antioxidative (tissue-protective) effects in patients with active pulmonary tuberculosis	Phase 2, Brazil	NCT03281226
Azithromycin	Adjunctive HDT with standard or MDR tuberculosis regimens to treat pulmonary tuberculosis – for reducing overt inflammation in patients' lungs (and potentially systemic inflammation also)	Phase 2, Netherlands	NCT03160638
Everolimus, auranofin, colecalciferol (INN on Martindale is colecalciferol [when referring to its use as a drug use colecalciferol, but when referring to the natural occurrence within the body, use vitamin D3], or CC-11050)	Adjunctive HDT with 2 months of isoniazid, rifabutin, pyrazinamide, and ethambutol followed by 4 months of isoniazid and rifabutin (modified drug regimen) to improve treatment efficacy and clinical outcomes in pulmonary tuberculosis	Phase 2, South Africa	NCT02968927
Mycobacterium indicus pranii	Used as an immunomodulatory treatment to induce beneficial effects in patients with pulmonary tuberculosis following antibacterial therapy	Phase 3, India	NCT00265226
Colecalciferol	Used as a supplement to help resolve inflammation or to induce productive intracellular defence mechanisms – i.e., antimicrobial peptide production; multiple colecalciferol doses are assessed	Several intermediate to advanced clinical trials (phases 2–4), South Africa, India, UK	NCT03011580 NCT01992263 NCT02880982 NCT02169570
Dexamethasone	Adjunctive corticosteroid used as an anti-inflammatory drug to resolve cytokine storm and tissue destruction in patients with tuberculosis, including tuberculous meningitis	2 phase 3 trials, Vietnam and Indonesia	NCT03100786 (Vietnam); NCT03092817 (Indonesia)

Nitazoxanide	Tested in clinical trials for early antimycobacterial activity; however, nitazoxanide might also exert its effects via autophagy, as shown in a preclinical study82	Phase 2, Haiti	NCT02684240
Nyaditum Resae®	Heat-killed *Mycobacterium manresesis* to induce generation of memory regulatory T cells as a mechanism of avoiding overt tuberculosis-associated inflammation; safety study in children; given as a probiotic capsule	Phase 1, Spain	NCT02581579
Recombinant human interleukin-2	Given subcutaneously to patients with MDR tuberculosis as adjunct to standard chemotherapy for modulating T-cell activity	Phase 2/3, China	NCT03069534
GX-70	Safety study of DNA vaccine combining genes encoding *Mycobacterium tuberculosis* antigens as well as the human Flt3 ligand for immunomodulation in patients with tuberculosis who did not respond to treatment or experienced disease relapse	Phase 1, Korea	NCT03159975
Etoricoxib with or without H56:IC31 E	Etoricoxib is a COX2 inhibitor, and can increase the production of the anti-inflammatory lipid mediator prostaglandin E2; combination of etoricoxib and H56:IC31 (subunit vaccine with adjuvant) is expected to reduce non-specific inflammation while inducing targeted antituberculosis immune responses; assessed in patients with MDR tuberculosis	Phase 1, Norway	NCT02503839

HDTs: host-direct therapies; MDR: multidrug-resistant.

Search strategy and selection criteria

We searched reports published in English between Nov 1, 2014, and Feb 15, 2018, on Google, Google Scholar, PubMed, and ClinicalTrials.gov using the search keywords "tuberculosis", "multi-drug-resistant (MDR)-tuberculosis", "extensively-drug-resistant (XDR)-tuberculosis", "latent tuberculosis", "drugs", "trials", "host-directed therapy", "host-directed therapies", "biological therapies", "immune-based therapies", "prevention", "tuberculosis" plus "clinical trials", and "drug development". Individual searches were done for "Q203", "SQ109", "PBTZ169", "bedaquiline", "delamanid", "clofazimine", "levofloxacin", "moxifloxacin", "pretomanid", "pyrazinamide", "rifapentine", "rifampicin", "linezolid", "delpazolid", and "sutezolid". We reviewed information on new drugs, compounds, and clinical trials from the WHO Global Tuberculosis Report, 2017, websites of the TB Alliance, Unitaid, Critical Path to TB Drug Regimens, Treatment Action Group, and Stop TB Partnership Working Group for New TB Drugs. We selected relevant search results and analysed them in a non-systematic manner. We collated and synthesised information on the development of new tuberculosis drugs, treatment regimens, and host-directed therapies through communications with various stakeholders, including a review of presentations and abstracts at the International Union Against Tuberculosis and Lung Disease, Guadalajara, Mexico (Oct 11–14, 2017).

Zileuton, a 5-LOX inhibitor, approved for use in asthma, increases prostaglandin E2 (PGE2) and inhibits leukotrienes to limit type 1 interferon-mediated lung pathology, and it improves survival of *M tuberculosis*-infected mice.[97] The eicosanoid pathway thus represents a complex target for tuberculosis HDTs since the effect appears to be dependent on the stage of *M tuberculosis* disease.[98] Therefore, dinoprostone (i.e., prostaglandin E2) administration or zileuton might be an appealing HDT strategy during early infection given their enhancement of phagocyte-mediated immunity. However, considering its impairment of type-1 T-helper immunity, prostaglandin E2 inhibition might show an effect at later stages of disease. Information about the timing and benefit of eicosanoid modulators as HDT will be available from an ongoing clinical trial in Norway, which is assessing the therapeutic effect of adding etoricoxib as an adjunct to tuberculosis treatment (Table 2.5).

In addition to lipid-lowering properties, statins possess potent anti-inflammatory activities[99] and might reduce risk of tuberculosis.[100] Statin use by people newly diagnosed with type 2 diabetes did, however, not prevent development of tuberculosis.[101] Ezetimibe, a cholesterol absorption inhibitor, reduced *M tuberculosis* survival in cells from individuals with diabetes (oneline appendix). As adjunctive therapy in murine tuberculosis, statins shorten the time to culture negativity by 1 month, reduce tissue pathology, decrease culture-positive relapse, and enhance bacterial killing.[102,103] Further studies are required to assess drug interactions with first-line antituberculosis regimens and other medications, with detailed examination of adverse events related to cholesterollowering drugs, to support clinical translation.

Inhibitors of phosphodiesterase 3, phosphodiesterase 4, and phosphodiesterase 5, such as cilostazol, roflumilast, sildenafil, and tadalafil, increase the amount of cyclic AMP or cyclic

GMP and show promise as cancer immunotherapy.[104,105] In murine and rabbit models of tuberculosis, phosphodiesterase inhibitors accelerate lung sterilisation, reduce lung inflammation, and promote lung repair by potentiating isoniazid bactericidal activity, limiting tumour necrosis factor (TNF) α production, and reducing macrophage activation.[106,107] An interventional trial recruiting in South Africa is investigating the phosphodiesterase 4 inhibitor CC–11050, as HDT in conjunction with the full tuberculosis regimen. Similarly, CC–3052 delivered promising results in a tuberculosis model in mice (online appendix).

Cancer drugs, such as tyrosine kinase inhibitors,[108] are being repurposed as HDTs for tuberculosis treatment in preclinical murine models. Imatinib reduces *M tuberculosis* bacterial load and lung pathology, probably through the enhancement of autophagy, phagosomal acidification, and myeloid cell mobilisation.[109,110] Imatinib is being assessed for its safety and immunogenicity in a phase 1 trial. The tyrosine kinase inhibitor gefitinib and janus kinase inhibitor tofacitinib, also yield similar findings to imatinib and warrant prospective clinical trial investigations (online appendix).

Metformin, a drug used for type 2 diabetes, activates AMP-activated protein kinase, which regulates the amount of cellular energy, T-cell differentiation, and development of memory.[111] Metformin reduces bacterial burden and ameliorates lung pathology in mice and human beings by enhancing autophagy and increasing production of reactive oxygen species.[83,112] The use of metformin as adjunctive treatment, however, did not improve sterilising activity and tuberculosis relapse in patients with diabetes who also had tuberculosis.[113] The surge in cellular and immune-metabolism research will yield several new HDT candidates, which will require careful assessment in preclinical models before being tested in human beings. Several factors require investigation before introducing metformin to tuberculosis treatment regimens, including pharmacokinetics and drug–drug interactions in the context of HIV.

Immunomodulatory biologics

Immune checkpoint inhibitors (ICIs), such as monoclonal antibodies nivolumab (acts against programmed death [PD] 1) and ipilimumab (acts against cytotoxic T-lymphocyte–associated antigen 4 [CTLA4]), have been successfully used for treatment of various cancers.[114] Signalling via immune checkpoints inhibits T-cell and B-cell function[115] and in tuberculosis, these immune regulatory checkpoints are perturbed and linked to T-cell exhaustion.[116] Inhibition of CTLA4 enhances immune responses in murine tuberculosis, albeit without improving bacillary clearance. CTLA4 polymorphisms are linked to tuberculosis susceptibility in several population groups.[117] Inhibition of the PD1–PD-ligand1 pathway enhances *M tuberculosis*-specific responses in human peripheral blood mononuclear cells.[118] However,

case reports caution that ICIs can result in the development of active tuberculosis, probably due to excessive inflammation and increased focal necrosis.[119] The use of ICIs, which block the PD1–PD-L1 pathway, as adjunct HDTs with tuberculosis therapy, should be viewed in light of such potential deleterious consequences. This treatment will require further assessment with regards to method, dose, and timing in animal models that closely reflect human lung pathology.

Vitamin D3 deficiency is a risk factor for development of tuberculosis[120] and its use as adjunct HDT treatment has yielded varying outcomes. Although some trials showed enhanced clinical and radiographic improvement, host immune activation,[121] and accelerated time to sputum conversion,[122] other studies have not.[123] Ongoing trials (Table 2.5) take into consideration several variables, such as differing concentrations of baseline serum vitamin D3, dietary intake, and therapeutic dosage of colecalciferol.

Vitamin A might have host immunomodulatory potential and in vitro antimycobacterial capabilities.[124] In one study, vitamin A deficiency was associated with risk of incident tuberculosis in household contacts, and cosupplementation of retinol with zinc improved tuberculosis treatment outcomes.[125] However, this result has not been supported by other studies. The difference in results might be due to different methods of determining vitamin A status, which requires measurements of serum retinol concentrations.[126] In a murine model of tuberculosis the active derivative of vitamin A, all-transretinoic acid, has shown potential for decreasing in vitro *M tuberculosis* burden and reducing relapse rates (online appendix).[127]

Cellular therapy has shown promise in the cancer field, and it is being extrapolated for use as adjunct therapy for individuals with drug-resistant tuberculosis.[128,129] Mesenchymal stromal cells (MSCs) have immunomodulatory and antibacterial properties[130] that improve peripheral blood immune responses and lung pathology in human and murine tuberculosis.[130,131] The effects of MSCs at local sites of disease require definition.[132] Modulation of immune regulatory cells, with low-dose cyclophosphamide chemotherapy, can reduce circulating regulatory T cells and might allow for effective cellular immune responses to be established. In murine tuberculosis, T-cell adoptive transfer in the lungs did not substantially accelerate mycobacterial clearance, although gamma delta (γδ) T-cell transfer resulted in reduced bacterial dissemination in non-human primates (online appendix). Further studies are required of interventional T-cell therapy as an HDT, for treating tuberculosis. Myeloid-derived suppressor cells (MDSCs) are increased in human and murine tuberculosis, display T-cell immunosuppressive properties,[132–134] and harbour *M tuberculosis*. Ongoing

clinical trials targeting MDSC in cancer,[135–137] and preclinical evidence from the tuberculosis mouse model with denileukin diftitox, suggest MDSCs as a focus for investigations (online appendix).

Micro RNA (miRNAs) are small non-coding RNAs that regulate gene expression and can affect host immunity to *M tuberculosis* infection through modulation of inflammation, TNFα, interleukin-6, chemokines, and stimulation of macrophage polarisation.[138,139] Evidence is emerging that suggests miRNAs could serve as cancer immunotherapy. Fundamental research, including the functional role of several miRNAs – e.g., miRNA-223, miRNA-21, and miRNA-29 – and their relationship to cavity tuberculosis, should be expanded to establish their value as potential therapeutic targets in tuberculosis.[140,141]

Although TNFα is essential to granuloma formation, macrophage antimicrobial activity, and killing of *M tuberculosis* mediated by reactive oxygen species,[142] TNFα can also trigger cell necrosis and exacerbate inflammation, paradoxically exacerbating pathology.[143] TNFα inhibition destabilises granulomas, reactivates *M tuberculosis* bacilli in patients with latent *M tuberculosis* infection, and increases the risk of tuberculosis progression. Therefore, drugs that block TNFα require assessment as adjunctive HDT.[144,145] Cytokine supplementation with interferon gamma has shown variable efficacy and nominal benefit in drugsensitive[146] and drug-resistant tuberculosis.[147] These studies underscore the complexity of the use of cytokines as HDTs. Trials investigating recombinant interleukin-2 treatment in patients with drug-resistant tuberculosis are ongoing (Table 2.5).

Future HDT research

Although several HDTs show promise in preclinical studies, further research is required to assess the effect of HDTs on key immune functions during different phases of *M tuberculosis* infection and disease. The timing of specific HDTs might be crucial since proinflammatory and anti-inflammatory immune mechanisms have important roles during different stages of tuberculosis. The use of companion biomarker studies (i.e., circulating cytokines), expression of cell-surface molecules (immune checkpoints, chemokine receptors, signalling molecules), existing pharmacological data, and safety and efficacy profiles based on previous clinical studies in other modalities (i.e., cancer, autoimmune diseases), will help select the most promising HDT strategies for clinical investigation in tuberculosis. Assessment of new HDTs in trials should be undertaken in different geographical and clinical settings, and they should include safety, kinetic studies, mechanisms of action, disease severity, and impact studies.

Conclusions

Steady progress is being made in the development of new and repurposed tuberculosis drugs, treatment trials, and HDTs. Several new or repurposed drugs are being studied for improved management of drug-susceptible and MDR tuberculosis. A range of candidate HDTs and immune-based treatments are being investigated as adjunct therapy. Development of tuberculosis drugs and HDTs, and access to them, is hampered by inadequate funding. Another big challenge is ensuring that these treatments are affordable, effective, safe, and reach the people who need them.

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Chapter 3

Comparison of effectiveness and safety of imipenem/clavulanate versus meropenem/clavulanate containing regimens in the treatment of MDR and XDR-TB

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Summary

No large study to date has ever evaluated the effectiveness, safety, and tolerability of imipenem/clavulanate (IC) vs. meropenem/clavulanate (MC) to treat multidrug-resistant (MDR-) and extensively drug-resistant tuberculosis (XDR-TB). Aim of this observational study is to compare the therapeutic contribution of IC vs. MC added to background regimens to treat MDR- and XDR-TB cases.

84 patients treated with IC-containing regimens showed similar median number of antibiotic resistances (8 vs. 8) but more fluoroquinolone resistance (79.0% vs. 48.9%; $p<0.0001$) and higher XDR-TB prevalence (67.9% vs. 49.0%; $p=0.01$) in comparison with 96 patients exposed to MC-containing regimens. Patients were treated with an IC- and MC-containing regimens for a median of 187 (60–428) vs. 85 (49–156) days, respectively.

Statistically significant differences were observed on sputum smear and culture conversion rates (79.7% vs. 94.8%, $p=0.02$, and 71.9% vs. 94.8%; $p<0.0001$, respectively) and on success rates (59.7% vs. 77.5%; $p=0.03$). Adverse events to IC and MC were reported in 5.4% and 6.5% of cases only.

Our study suggests that MC is more effective than IC in treating M/XDR-TB patients.

Introduction

Over 480,000 new multidrug-resistant tuberculosis (MDR-TB) cases and 190,000 deaths have been estimated to occur in 2014 by the World Health Organization (WHO), with only one MDR-TB case out of four being currently diagnosed and treated.[1] Half of the 123,000 cases of MDR-TB notified to WHO in 2014 occurred in India, Russian Federation, and South Africa. Globally, 3.3 out of 100 new cases and 1 out of 5 previously treated cases of TB harbour MDR-TB strains of *Mycobacterium tuberculosis*. While overall 9.7% of the MDR-TB strains met the criteria defining extensively drug-resistant TB (XDR-TB, e.g. resistance to at least one fluoroquinolone and a second line-injectable drug) in some of the former Soviet Union countries this proportion is much higher (29% in Belarus, 15% in Latvia and 15% in Georgia).[1,2]

Recent evidence shows that treating MDR- and XDR-TB patients with the drugs available today is long, expensive, complicated, and adverse events frequent.[3-8]

Presently a stepwise approach in the use of second-line anti-TB drugs (which are classified into five groups) is recommended by WHO.[7,9]

The main difficulty faced by clinicians treating MDR- and XDR-TB cases is to identify at least 4 active drugs which are necessary to design an effective multi-drug regimen as per WHO guidelines.[3,4,7,10,11] New drugs like delamanid[12-14] and bedaquiline,[15-20] and a few re-purposed drugs (presently included in the WHO Group 5, i.e., drugs with unknown/limited evidence on efficacy and/or tolerability) are presently attracting scientific interest;[7,21] among them linezolid[10,22-28] and carbapenems.[29-34] As of today, the carbapenem group of drugs, which includes meropenem, imipenem and ertapenem, are used to treat MDR-/XDR-TB cases, although the evidence available on their efficacy, safety, and tolerability is extremely limited.[29-34]

The effectiveness of β-lactam antibiotics is unfortunately limited, as *M. tuberculosis* is protected through its potent β-lactamase, encoded by the BlaC gene.[35,36] Recent studies indicate that clavulanate (a β-lactamase inhibitor) can inhibit the activity of BlaC-coded products in vitro.[36] Meropenem, offering a limited substrate to hydrolysis, has shown high bactericidal in vitro activity in association to clavulanate against *M. tuberculosis* (susceptible, MDR- and XDR-TB strains) as well as the in vivo ability to sterilize cultures within 2 weeks.[37,38] Moreover, a study suggested synergy with amoxicillin and meropenem.[39] This has been confirmed in a murine model.[40] Its effectiveness, initially suggested in two case reports of 10 cases or less,[30,41] has been then confirmed by two case-control studies. The

first, with a limited sample size (37 patients at a single centre) suggested the drug was effective (offering up to 20–30% sterilising power) and well tolerated.[29] The second more recent study, was conducted by the International Carbapenems Study Group (ICSG, formerly the European Carbapenems Study Group) in 17 centres and 6 countries in Europe and Latin America with over 90 cases. It confirmed that MC is safe and that the activity of the drug combination is promising, as non-different (non-inferior) sputum smear conversion, culture conversion and treatment success rates between cases and controls have been identified despite controls had a much less severe resistance pattern than MC-treated cases.[42]

Evidence on IC is even more limited, consisting in a series of 10 patients and one case-report.[33,34]

Recently, the TB reference centres belonging to the ICSG[31,42] conducted a large observational study evaluating the therapeutic contribution of IC added to a background regimen (as per WHO guidelines) when treating MDR- and XDR-TB cases.

Aim of the present study is to compare the effectiveness, safety, and tolerability profile of MC and IC in a large observational cohort of MDR-TB patients.

Material and methods

The methodological characteristics were previously described.[42] MDR-TB reference centres located in European and Southern American countries retrospectively recruited culture-confirmed MDR-TB patients aged ≥15 years. An MDR-TB case was defined as an individual with TB caused by *M. tuberculosis* strains phenotypically resistant to at least isoniazid and rifampicin. Patients were consecutively selected on the basis of their exposure to MC and IC during their intensive and/or continuation phase.

An individualized TB regimen was administered following the results of the DST carried out by externally quality-assured laboratories.[11] The attending physician prescribed anti-TB drugs without any compelling criteria of experimental protocols and, consequently, blinding or randomized methods were not followed. MC was administered at a daily dosage of meropenem 1 g three times a day intravenously plus amoxicillin/clavulanic acid 1.2 g three times a day. The only exception was represented by the Belgium centre where meropenem was prescribed at a daily dosage of 2 g three times a day (17/180, 9.4%). IC was administered at a dose of 500 mg of imipenem four times a day plus amoxicillin/clavulanic acid as above.

Standardized ad-hoc e-forms were prepared to collect epidemiological (i.e., duration of hospital stay, age, place of birth, sex, residence, immigration from a TB high-burden country), clinical (i.e., HIV status, administration of HIV drugs, previous TB diagnosis and treatment, previous treatment outcomes, radiological findings, TB therapy and related adverse events, duration of exposure to MC and IC, surgery, sputum smear and culture positivity at the treatment baseline, at 30, 60 and 90 days, time to sputum smear and culture conversion, WHO treatment outcomes), and microbiological (i.e., DST results) information from official medical files.

Ethical approval for the collection and analysis of anonymous and retrospective data and for the compassionate use of the drugs was obtained by the institutional review boards of the participating institutions as per legislation in force in the different ICSG countries and at the coordinating centre.

Qualitative and quantitative variables were summarized with percentages and means (standard deviations – SD) or medians (interquartile ranges – IQR) depending on their normality. Chi-square or Fisher's exact and the Mann-Whitney tests were adopted to compare qualitative and quantitative variables, respectively. Differences in terms of sputum smear and culture conversions between IC and MC groups were assessed with a survival analysis and a log-rank test. A p-value of less <0.05 (two-tailed) was considered statistically significant. Statistical computations were performed with Stata 13.0 (StataCorp, College Station, TX).

Results

A total of 180 MDR-TB patients were selected for the analysis: 96 (53.3%) exposed to MC and 84 (46.7%) to IC (Table 3.1).

The prevalent gender of the cohort was male (105, 58.3%) and the median (IQR) age was 35 (26–45) years (Table 3.1).

Migrants coming from high TB prevalence countries were 100 (55.6%), whereas only a low proportion (5.8%) was HIV-infected. A higher proportion of migrants (76.0% VS. 32.1%; $p<0.0001$) and of patients born in Europe (75.0% VS. 45.2%; $p<0.0001$) was observed in the MC treated group (Table 3.1).

Pulmonary TB was diagnosed in 176 out of 179 (98.3%) cases. The proportion of sputum smear and culture positive cases was 89.4% and 97.8%, respectively (Table 3.2).

Table 3.1: Demographic, epidemiological, and clinical characteristics of M/XDR-TB patients treated with MC- vs IC-containing regimens

Variables	Total subjects	Meropenem/ Clavulanate-containing regimen	Imipenem/ Clavulanate containing regimen	p-value
Admission year, n (%)				<0.0001
2005	2/180 (1.1)	0/96 (0.0)	2/84 (2.4)	
2006	3/180 (1.7)	0/96 (0.0)	3/84 (3.6)	
2007	6/180 (3.3)	0/96 (0.0)	6/84 (7.1)	
2008	9/180 (5.0)	2/96 (2.1)	7/84 (8.3)	
2009	11/180 (6.1)	7/96 (7.3)	4/84 (4.8)	
2010	16/180 (8.9)	15/96 (15.6)	1/84 (1.2)	
2011	27/180 (15.0)	26/96 (27.1)	1/84 (1.2)	
2012	20/180 (11.1)	9/96 (9.4)	11/84 (13.1)	
2013	34/180 (18.9)	6/96 (6.3)	28/84 (33.3)	
2014	36/180 (20.0)	25/96 (26.0)	11/84 (13.1)	
2015	16/180 (8.9)	6/96 (6.3)	10/84 (11.9)	
Age at the admission years, median (IQR)	35 (26–45)	34 (26–43)	36 (27–46)	0.37
Males, n (%)	105/180 (58.3)	54/96 (56.3)	51/84 (60.7)	0.54
Country of birth, n (%)				<0.0001
Africa	7/180 (3.9)	5/96 (5.2)	2/84 (2.4)	
Asia	6/180 (3.3)	3/96 (3.1)	3/84 (3.6)	
Europe	110/180 (61.1)	72/96 (75.0)	38/84 (45.2)	
Other geographical areas	57/180 (31.7)	16/96 (16.7)	41/84 (48.8)	
Migrant, n (%)	100/180 (55.6)	73/96 (76.0)	27/84 (32.1)	<0.0001
HIV-infected, n (%)	10/173 (5.8)	8/89 (9.0)	2/84 (2.4)	0.10
Exposure to ART, n (%)	8/10(80.0)	6/8(75.0)	2/2 (100.0)	0.15
Previous exposure to anti-TB therapy, n (%)	143/179 (79.9)	66/95 (69.5)	77/84 (91.7)	<0.0001
Number of times treated >1 month, median (IQR)	2 (1–3)	2 (1–4)	2 (1–3)	0.98
Surgical treatment, n (%)	32/176 (18.2)	14/92 (15.2)	18/84 (21.4)	0.29
Prior treatment outcome, n (%)				0.006
Failed	117/140 (83.6)	49/62 (79.0)	68/78 (87.2)	
Default	11/140 (7.9)	5/62 (8.1)	6/78 (7.7)	
Completed	3/140 (2.1)	2/62 (3.2)	1/78 (1.3)	
Cured	5/140 (3.6)	5/62 (8.1)	0/78 (0.0)	
Transferred out	0/140 (0.0)	0/62 (0.0)	0/78 (0.0)	
Relapse	1/140 (0.7)	1/62 (1.6)	0/78 (0.0)	
Unknown	2/140 (1.4)	0/62 (0.0)	2/78 (2.6)	
Form, n (%)				<0.0001
New	40/179 (22.4)	32/96 (23.0)	8/83 (9.6)	
Relapse	18/179 (10.1)	13/96 (13.5)	5/83 (6.0)	
Chronic	16/179 (8.9)	15/96 (15.6)	1/83 (1.2)	
Failure	104/179 (58.1)	36/96 (37.5)	68/83 (81.9)	
Unknown	1/179 (0.6)	0/96 (0.0)	1/83 (1.2)	

Table 3.1 continues on next page.

Table 3.1: ***Continued***

Variables	Total subjects	Meropenem/ Clavulanate-containing regimen	Imipenem/ Clavulanate containing regimen	p-value
Pulmonary TB, n (%)	176/179 (98.3)	93/96 (96.9)	83/83 (100.0)	0.25
Extra-pulmonary TB, n (%)	18/179 (10.1)	14/96 (14.6)	4/83 (4.8)	0.04
Radiological fi ndings, n (%)				0.01
Cavitary lesions	44/176 (25.0)	16/93 (17.2)	28/83 (33.7)	
Bilateral pulmonary involvement with cavitary lesions	95/176 (54.0)	50/93 (53.8)	45/83 (54.2)	
Bilateral pulmonary involvement	22/176 (12.5)	16/93 (17.2)	6/83 (7.2)	
Non-cavitary non-bilateral pulmonary involvement	15/176 (8.5)	11/93 (11.8)	4/83 (4.8)	
Sputum smear positive, n (%)	161/180 (89.4)	85/96 (88.5)	76/84 (90.5)	0.67
Sputum culture positive, n (%)	174/178 (97.8)	96/96 (100.0)	78/82 (95.1)	0.04
Streptomycin resistance, n (%)	141/155 (91.0)	76/80 (95.0)	65/75 (86.7)	0.09
Ethambutol resistance, n (%)	140/175 (80.0)	80/95 (84.2)	60/80 (75.0)	0.13
Pyrazinamide resistance, n (%)	122/159 (76.7)	84/94 (89.4)	38/65 (58.5)	<0.0001
Fluoroquinolone resistance, n (%)	110/175 (62.9)	46/94 (48.9)	64/81 (79.0)	<0.0001
Ethionamide resistance, n (%)	111/155 (71.6)	63/86 (73.3)	48/69 (69.6)	0.61
Cycloserine resistance, n (%)	42/143 (29.4)	15/75 (20.0)	27/68 (39.7)	0.01
Amikacin resistance, n (%)	67/136 (49.3)	40/82 (48.8)	27/54 (50.0)	0.89
PAS (p-aminosalicylic acid) resistance, n (%)	43/106 (40.6)	23/47 (48.9)	20/59 (33.9)	0.12
Capreomycin resistance, n (%)	77/142 (54.2)	38/81 (46.9)	39/61 (63.9)	0.04
Kanamicin resistance, n (%)	84/137 (61.3)	37/75 (49.3)	47/62 (75.8)	0.002
Linezolid resistance, n (%)	5/83 (6.0)	4/75 (5.3)	1/8 (12.5)	0.41
Rifabutin, resistance n (%)	37/45 (82.2)	25/26 (96.2)	12/19 (63.2)	0.006
Other resistances, n (%)	10/18 (55.6)	6/11 (54.6)	4/7 (57.1)	1.00
Number of resistances, median (IQR)	8 (6–9)	8 (6–9)	8 (7–8)	0.34
Length of hospital stay days, median (IQR)	129 (68–206)	101 (61–172)	164 (110–247)	0.0001
Months of treatment after MDR-TB diagnosis, median (IQR)	18 (12–24)	18 (18–22)	18 (9–24)	0.24
XDR, n (%)	104/180 (57.8)	47/96 (49.0)	57/84 (67.9)	0.01
Moxifloxacin, n (%)	145/179 (81.0)	77/95 (81.1)	68/84 (81.0)	0.99
Levofloxacin, n (%)	20/180 (11.1)	9/96 (9.4)	11/84 (13.1)	0.43
Linezolid, n (%)	97/166 (58.4)	50/90 (55.6)	47/76 (61.8)	0.41
Delamanid, n (%)	1/175 (0.6)	1/95 (1.1)	0/80 (0.0)	1.00
Bedaquiline, n (%)	16/176 (9.1)	9/95 (9.5)	7/81 (8.6)	0.85

MDR-TB: multidrug-resistant tuberculosis; XDR-TB: extensively drug-resistant tuberculosis; MC: meropenem/clavulanate; IC: imipenem/clavulanate; IQR: interquartile range; ART: anti-retroviral therapy.

Table 3.2: Treatment outcomes of M/XDR-TB patients treated with Meropenem/Clavulanate- vs Imipenem/Clavulanate-containing regimens

Variables	Total subjects	Meropenem/ clavulanate-containing regimen	Imipenem/clavulanate-containing regimen	p-value
Sputum smear conversion, n (%)	106/122 (86.9)	55/58 (94.8)	51/64 (79.7)	0.02
Sputum smear conversion at 30 days of treatment, n (%)	89/178 (50.0)	37/94 (39.4)	52/84 (61.9)	0.003
Sputum smear conversion at 60 days of treatment, n (%)	116/170 (68.2)	59/91 (64.8)	57/79 (72.2)	0.31
Sputum smear conversion at 90 days of treatment, n (%)	132/165 (80.0)	76/90 (84.4)	56/75 (74.7)	0.12
Sputum smear conversion in patients with <8 resistances, n (%)	48/51 (94.1)	24/24 (100.0)	24/27 (88.9)	0.24
Sputum smear conversion in patients with ≥8 resistances, n (%)	58/71 (81.7)	31/34 (91.2)	27/37 (73.0)	0.07
Sputum smear conversion in MDR-TB patients, n (%)	49/53 (92.5)	33/33 (100.0)	16/20 (80.0)	0.02
Sputum smear conversion in XDR-TB patients, n (%)	57/69 (82.6)	22/25 (88.0)	35/44 (79.6)	0.52
Sputum culture conversion, n (%)	101/122 (82.8)	55/58 (94.8)	46/64 (71.9)	<0.0001
Sputum culture conversion at 30 days of treatment, n (%)	56/166 (33.7)	30/94 (31.9)	26/72 (36.1)	0.57
Sputum culture conversion at 60 days of treatment, n (%)	105/169 (62.1)	59/93 (63.4)	46/76 (60.5)	0.70
Sputum culture conversion at 90 days of treatment, n (%)	123/165 (74.6)	72/91 (79.1)	51/74 (68.9)	0.14
Sputum culture conversion in patients with <8 resistances, n (%)	46/51 (90.2)	24/24 (100.0)	22/27 (81.5)	0.05
Sputum culture conversion in patients with ≥8 resistances, n (%)	55/71 (77.5)	31/34 (91.2)	24/37 (64.9)	0.01
Sputum culture conversion in MDR-TB patients, n (%)	46/53 (86.8)	33/33 (100.0)	13/20 (65.0)	0.001
Sputum culture conversion in XDR-TB patients, n (%)	55/59 (79.7)	22/25 (88.0)	33/44 (75.0)	0.23
Days from start of anti-TB therapy to sputum smear conversion, median (IQR)	36 (30-60)	45 (28–68)	30 (30–60)	0.71
Days from start of anti-TB therapy to culture conversion, median (IQR)	52 (30-90)	44 (28–75)	60 (30–90)	0.05

Treatment outcome, n (%)				<0.0001
Cured	52/180 (28.9)	22/96 (22.9)	30/84 (35.7)	
Treatment completed	37/180 (20.6)	33/96 (34.4)	4/84 (4.8)	
Still on treatment	47/180 (26.1)	24/96 (25.0)	23/84 (27.4)	
Died	25/180 (13.9)	10/96 (10.4)	15/84 (17.9)	
Default	11/180 (6.1)	5/96 (5.2)	6/84 (7.1)	
Failure and died	6/180 (3.3)	1/96 (1.0)	5/84 (6.0)	
Transferred out	2/180 (1.1)	1/96 (1.0)	1/84 (1.2)	
Treatment success, n (%)	89/128 (69.5)	55/71 (77.5)	34/57 (59.7)	0.03
Treatment success in patients with <8 resistances, n (%)	41/60 (68.3)	24/34 (70.6)	17/26 (65.4)	0.67
Treatment success in patients with ≥8 resistances, n (%)	48/68 (70.6)	31/37 (83.8)	17/31 (54.8)	0.007
Treatment success in MDR-TB patients, n (%)	45/55 (81.8)	33/37 (89.2)	12/18 (66.7)	0.06
Treatment success in XDR-TB patients, n (%)	44/73 (60.3)	22/34 (64.7)	22/39 (56.4)	0.47

MDR-TB: multidrug-resistant tuberculosis; XDR-TB: extensively drug-resistant tuberculosis; IQR: interquartile range.

More than half were affected by XDR-TB (57.8%; 67.9% and 49.0% in the IC and MC group, respectively, p=0.01), but the median number of drug resistances was similar (8 vs. 8 in the MC and IC group, respectively; p=0.34) (Table 3.2).

Over 3 quarters of cases were previously treated for drug-susceptible or –resistant TB; however, patients exposed to IC-containing regimens had been treated more frequently for a previous TB diagnosis (91.7% VS. 69.5%; p<0.0001). However, the median number of previous anti-TB treatments was similar in the MC- and IC-treated groups [2 (1–4) VS. 2 (1–3)] (Table 3.1).

The prevalence of resistance to any fluoroquinolone was significantly higher among the IC-treated cases (79.0% vs 48.9%; p<0.0001); moreover a higher prevalence of resistance to capreomycin (63.9% vs. 46.9%; p=0.04) and kanamycin (75.8% vs 49.3%; p<0.002) was observed in comparison to the MC-treated group. The prevalence of resistance to amikacin was similar in both groups (50.0% vs. 48.8%, respectively) (Table 3.1).

Patients were treated with MC- and IC-containing regimens for a median (IQR) of 85 (49–156) and 187 (60–428) days) (Table 3.3). Adjuvant surgical therapy was performed in 18.2% of the cases.

Sputum smear and culture conversion rates were significantly higher in those exposed to MC (94.8% and 94.8%, respectively) than in those exposed to IC (79.7% and 71.9%; p=0.02 and p<0.0001, respectively). Similar proportional differences for the culture conversion were achieved when subgroup analyses were performed according to MDR-TB/XDR-TB status and the median number of drug resistances (i.e., ≥8 drug resistances) (Table 3.2).

The time to culture conversion was shorter in the MC- than in the IC-treated group [44 (28–75) vs. 60 (30–90) days; p=0.05] (Table 3.2, Figure 3.1).

Overall, cases treated with MC achieved higher statistically significant success rates than those treated with IC (77.5% vs. 59.7%; p=0.03) (Table 3.2).

Adverse events were reported only in 6 MC- (6.5%) and 3 (5.4%) IC-treated patients (p=1.0) (Table 3.3).

Table 3.3: Safety of Meropenem/Clavulanate- vs Imipenem/Clavulanate- containing regimens

Variables	Total subjects	Meropenem/Clavulanate-containing regimen	Imipenem/Clavulanate-containing regimen	p-value
Interruption of Linezolid, n (%)	39/139 (28.1)	23/90 (25.6)	16/49 (32.7)	0.37
Interruption of Linezolid due to adverse events, n (%)	25/131 (19.1)	14/82 (17.1)	11/49 (22.5)	0.45
AEs presumably due to Linezolid, n (%)	48/136 (35.3)	37/89 (41.6)	11/47 (23.4)	0.04
Anaemia, n (%)	29/141 (20.6)	20/92 (21.7)	9/49 (18.4)	0.64
Leukopaenia, n (%)	6/140 (4.3)	4/91 (53.9)	2/49 (4.1)	1.00
Thrombocytopaenia, n (%)	13/140 (9.3)	11/91 (12.1)	2/49 (4.1)	0.14
Peripheral neuropathy, n (%)	35 /139 (25.2)	29/91 (31.9)	6/48 (12.5)	0.01
Gastro-intestinal disorder, n (%)	17/140 (12.1)	8/91 (8.8)	9/49 (18.4)	0.10
Reversible adverse events, n (%)	64/91 (70.3)	44/63 (69.8)	20/28 (71.4)	0.88
Linezolid restarted if interrupted, n (%)	21/85 (24.7)	19/43 (44.2)	2/42 (4.8)	<0.0001
Total linezolid exposure, median (IQR)	239 (92–630)	173 (78–540)	288 (143–670)	0.03
Interruption of Meropenem-Imipenem, n (%)	67/150 (44.7)	52/94 (55.3)	15/56 (26.8)	0.001
Interruption of Meropenem-Imipenem due to AEs, n (%)	12/149 (8.1)	8/94 (8.5)	4/55 (7.3)	1.00
AEs presumably due to Meropenem-Imipenem, n (%)	9/149 (6.0)	6/93 (6.5)	3/56 (5.4)	1.00
Meropenem-Imipenem restarted if interrupted, n (%)	4/12 (33.3)	4/8 (50.0)	0/4 (0.0)	0.08
Total Meropenem-Imipenem exposure, median (IQR)	104 (109–298)	85 (49–156)	187 (60–428)	0.009

IQR: interquartile range; AEs: adverse events.

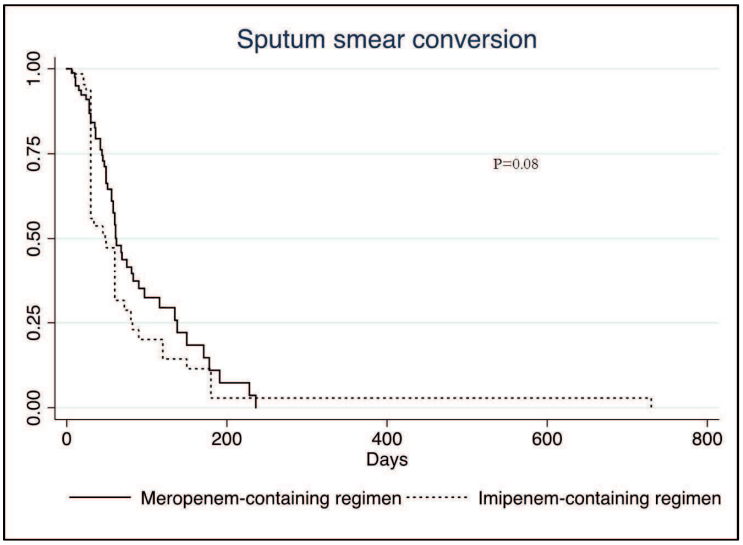


Figure 3.1: Sputum-smear conversion in MDR-TB patients treated with Meropenem/Clavulanate vs Imipenem/ Clavulanate-containing regimens.

Discussion

Aim of the present study was to retrospectively compare the effectiveness, safety, and tolerability profile of MC and IC in a large cohort of MDR-TB patients.

The results of our study demonstrated that, overall, the MC-containing regimens achieved better results than IC-containing ones. In particular, a) culture conversion rates were statistically higher (both in the whole cohort and in the MDR-TB sub-groups), b) the time to culture conversion was shorter and c) the treatment success rates were significantly higher (both in the overall cohort and in the patients with ≥8 resistances) in the MC- than in the IC-containing group.

Furthermore, the study demonstrated that both drugs were well tolerated, and the adverse events were rare (only 6.5% in the MC- and 5.4% in the IC-containing regimens).

This is, to our knowledge, the first study describing efficacy, safety and tolerability of IC-containing regimens and comparing the clinical performances of two of the core carbapenems (i.e., IC and MC) in a large cohort of MDR-TB patients in the scientific literature.

In a previous study of the same group[42] the performances of the MC-containing regimens were compared to a control group. The study results suggested that MC is active, as

MC-containing regimens achieved non-different results than the controls in spite of a much more severe resistance profile.

Although it is always difficult to attribute to MC and IC the causality of the results observed, we can underline that IC-containing regimens achieved bacteriological and treatment success rates comparable to those of other cohorts of MDR-TB cases,[3,4] while MC-containing-regimens had promising results (94.8% sputum smear and culture conversion, and 77.5% treatment success). In order to remove the 'background noise' caused by the observational design, the study findings need to be confirmed by randomized controlled clinical trials.

Based on the molecular mechanism of action, imipenem is more active than meropenem.[43] However, this does not necessarily translate into better clinical results. The pharmacokinetic-pharmacodynamic index, as well as the free drug concentration exceeding the minimal inhibitory concentration (MIC), could have favoured the group with the MC-containing regimens. In addition, synergy with the other anti-TB drugs could have been different for the carbapenems prescribed in this study.

As MC appears to be more active against *Mycobacterium tuberculosis* than IC, the former should be favoured in the treatment of MDR TB. Should MC be unavailable, higher doses of IC as per *Pseudomonas* infection could probably be administered (i.e., 1 g four times per day) given the drug is well tolerated.

Among the strengths of the study we mention the large size of the IC and MC cohorts and the detailed information collected from the participating centres in Europe and Latin America. The drug-resistance patterns, number of previous anti-treatment cycles as well as most of the demographic, epidemiological, and clinical variables did not differ significantly in the MC and IC cohorts.

However, the observational and retrospective design of the study determines several interpretational limitations. In particular we mention the missing pre-study definition of a sample size and the possibility to randomise and ensure blindness, which could increase the probability of a selection bias. Furthermore, the latter methodological issue is clearly highlighted by the higher prevalence of resistance to any fluoroquinolone in the IC cohort, as well as a higher prevalence of resistance to 2 out of 3 second-line anti-TB injectables (kanamycin and capreomycin). Furthermore, exposure to previous anti-TB treatment and proportion of previous treatment failures was higher in the IC cohort.

As MC seems to perform better, but IC is cheaper and more widely available, economic analyses will be important to finally assess the future role of these compounds.

However, the new information provided by this observational study allows clinicians managing difficult-to-treat TB cases to know how to use carbapenems and other re-purposed drugs in case the minimum number of active drugs necessary to design an effective regimen is lacking.[3,4,9,44-47]

In this context other second-line drugs like fluoroquinolones or clofazimine might contribute to cardiologic or other adverse events.[48] Unlike all of the above, the repurposed carbapenems are frequently well tolerated and offer few drug-drug interactions, and should the need arise can replace other TB drugs based on their advantageous safety and tolerability profile. The Authors believe that the benefits of β-lactam use for the treatment of TB outweighs the risks of further antimicrobial resistance.

Although new compounds will hopefully appear soon to support the move towards TB Elimination,[49] the carbapenems confirm to have a particular role. The Authors would recommend the use of MC in the intensive phase of treatment, particularly to manage the most severe cases until bacteriological conversion has been achieved. If active drugs are lacking to design an effective regimen in the continuation phase, ertapenem/clavulanate or faropenem/clavulanate could potentially be considered in the continuation phase. Given the widespread use of amoxicillin/clavulanic acid in the community, DST for meropenem/clavulanate is recommended before using the drug in a regimen.

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Chapter 4

Effectiveness and safety of meropenem/clavulanate containing regimens in the treatment of multidrug and extensively drug-resistant tuberculosis

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Summary

No large study has ever evaluated the efficacy, safety, and tolerability of meropenem/clavulanate (MC) to treat multidrug-resistant (MDR-) and extensively drug-resistant tuberculosis (XDR-TB). Aim of this observational study is to evaluate the therapeutic contribution, effectiveness, safety, and tolerability profile of MC added to a background regimen when treating MDR- and XDR-TB cases. Patients treated with MC-containing regimen (n=96) showed a greater drug-resistance profile than those exposed to a MC-sparing regimen (n=168): in the former group XDR-TB was more frequent (49% vs 6.0%; $p<0.0001$), and the median (IQR) number of antibiotic resistances was higher [8 (6–9) vs. 5 (4–6)]. Patients were treated with a MC-containing regimen for a median of 85 (49–156) days. No statistically significant differences were observed in the overall MDR-TB cohort and in the subgroups with and without the XDR-TB patients; in particular, sputum smear and culture conversion rates were similar in XDR-TB patients exposed to MC-containing regimens (88.0% vs. 100.0%, p=1.00, and 88.0% vs. 100.0%; p=1.00, respectively). Only 6 cases reported adverse events attributable to MC (4 of them then restarting it). The non-different outcomes and bacteriological conversion rate observed in cases who were more severe than controls might imply that MC could be active in treating MDR/XDR-TB cases.

Introduction

The World Health Organization (WHO) estimated that 480,000 new multidrug-resistant tuberculosis (MDR-TB) cases occurred globally in 2014, with 190,000 deaths.[1] Only one MDR-TB case out of three is currently diagnosed and one out of four treated.[1] Of the 123,000 cases of MDR-TB notified to WHO in 2014, about half were detected in India, Russian Federation, and South Africa. Overall 3.3% of new cases and 20% of previously treated cases of TB are MDR-TB. In Belarus, over 50% of TB cases are MDR-TB; 34% of new cases and 64% of those previously treated.[1,2] The proportion of MDR-TB cases harbouring XDR-TB strains of *Mycobacterium tuberculosis* in 2014 was highest in Belarus (29%), Georgia (15%), and Latvia (19%), and accounted for as much as 9.7% globally.[1,2]

Treatment of MDR-TB cases is long, expensive and associated with frequent adverse events.[3-8] Furthermore, a large proportion of patients with MDR-TB have additional drug resistances, and this makes the choice of an adequate treatment very difficult.

The WHO guidelines in force recommend the stepwise use of second-line drugs classified into five groups,[7] although modifications to drugs grouping have been recently proposed9 and discussion is ongoing at the WHO level.

The difficulty in identifying at least 4 active drugs, suitable for inclusion in a multi-drug regimen effective against these resistant forms of TB, makes the need for new antibiotics really urgent.[3,4,7,10,11]

Presently, there is a lot of interest on the new drugs like delamanid[12-14] and bedaquiline,[15-20] and in re-purposed drugs, which are included in the WHO Group 5, i.e., drugs with unknown/limited evidence on efficacy and/or tolerability.[7,21] This group includes linezolid[10,22-28] and carbapenems.[29-34] Carbapenems represent an interesting class of drugs (including meropenem, imipenem and ertapenem), which are widely used to treat MDR-/XDR-TB cases, although very limited evidence exists on their efficacy, safety, and tolerability.[29-34]

The association of a β-lactam antibiotic with a β-lactamase inhibitor, in fact, has been explored recently with apparently sub-optimal results, as *M. tuberculosis* is protected from β-lactam antibiotics through its potent β-lactamase, encoded by a gene called *BlaC*.[35,36] Clavulanate (a β-lactamase inhibitor) has a demonstrated capacity to inhibit the activity of *BlaC*-coded products in vitro.[36] Meropenem, a carbapenem offering a limited substrate to hydrolysis, has demonstrated high bactericidal in vitro activity when combined to clavulanate against susceptible, MDR- and XDR-TB strains of *M. tuberculosis* and the ability

to sterilize cultures in vivo within 2 weeks.[37,38] It has also shown promising activity in a murine model[39] and its clinical effectiveness against *M. tuberculosis*-related disease was proved in two case reports of 10 cases or less.[30,40] To date, a single study is available in the literature suggesting the drug is effective and well tolerated. Unfortunately, this study had a limited sample size of 37 patients recruited at a single centre and was focused on the evaluation of bacteriological conversion, without providing final treatment outcomes.[29]

Taking advantage of existing collaborations and established research protocols, TB reference centres belonging to the International Carbapenems Study Group (ICSG)[31] conducted a large observational study to evaluate the therapeutic contribution, effectiveness, safety, and tolerability profile of meropenem/clavulanate (MC) added to a background regimen (as per WHO guidelines) when treating MDR- and XDR-TB cases.

Material and methods

An observational, retrospective, cohort study was performed in 5 centres specialized in the management of MDR-/XDR-TB cases in 3 countries which decided to adhere to the ICSG project.

Individuals aged <15 years were excluded. Only adults with a culture-confirmed diagnosis of MDR-TB (i.e., TB caused by *M. tuberculosis* isolates resistant to at least isoniazid and rifampicin) were enrolled and evaluated according to MC exposure (time period of clinical evaluation ranges from 2003 to 2015).

Both individuals treated with an MDR-TB MC-containing and -sparing regimens were consecutively recruited following a retrospective design in all centres. Specifically, patients from each participating centre were separated in a group exposed and not exposed to MC.

Anti-TB drugs were prescribed following the WHO recommendations based on DST, provided by quality-assured laboratories serving all the participating centres without any blinding or randomization procedures.[11] MC was administered off-label at a dosage of 1 g tid (three times a day) intravenously (2 g tid in Belgium) and clavulanate in the form of oral amoxicillin/clavulanic acid. The ratio between those exposed and not exposed to MC-containing regimen was 1:2.

Demographic, epidemiological, clinical, microbiological variables were retrospectively collected from medical records using standardized ad-hoc e-forms. In particular, the following information were retrieved: date of admission, length of hospital stay, date and

place of birth, gender, residence, immigration from a TB high-burden country, HIV-status, exposure to antiretroviral drugs, previous TB diagnoses, previous anti-TB treatments (i.e., exposure to anti-TB drugs for more than one month) and previous treatment outcomes, DST results, including susceptibility or resistance to the drugs defining XDR-TB (i.e., TB caused by *M. tuberculosis* strains resistant to isoniazid, rifampicin, any fluoroquinolones, and at least one second-line injectable anti-TB drug: amikacin, capreomycin, kanamycin), radiological findings, anti-TB regimen administered (including dosage and length of exposure), surgery, duration of exposure to MC and other relevant drugs (e.g. linezolid) and adverse events potentially ascribed to the MC and other relevant drugs (i.e., linezolid), management of adverse events, proportion of sputum smear and culture positivity at the hospital admission and at 30, 60 and 90 days after the prescription of second-line anti-TB drugs, time to sputum smear/culture conversion and treatment outcomes.

A descriptive analysis of the qualitative and quantitative variables was performed using absolute and relative (percentages) frequencies and means±SD or median (interquartile ranges (IQR)) according to their parametric distribution, respectively. Inference analysis was carried out with the Chi-square or Fisher's exact tests and the Wilcoxon-Mann-Whitney test for categorical and numerical variables, respectively. Survival analyses were performed to assess the microbiological (i.e., sputum smear and culture) conversion in patients treated with MC-containing and -sparing regimens.

Two-tailed p-values were deemed statistically significant when $p<0.05$. All statistical analyses were carried out with the Stata 13.0 (StataCorp, College Station, TX).

Ethical approval for the collection and analysis of anonymous and retrospective data and for the compassionate use of the drugs was obtained by the institutional review boards of the participating institutions as per legislation in force in the different ICSG countries and at the coordinating centre.

Results

A retrospective cohort of 264 MDR-TB patients was recruited (Table 4.1). One fifth of them (21.6%) were affected by XDR-TB.

Ninety-six were treated with MC-containing and 168 with MC-sparing regimens. The majority (52.1%) of the patients were males, with a median age of 33 (IQR: 26–43) years, and most of them were migrants (76.5%), whose country of birth was located in the majority of the cases (61.4%) in Europe. Thirteen individuals (5.2%) were HIV-infected.

Table 4.1: Demographic, epidemiological, and clinical characteristics of M/XDR-TB patients treated with OBR with and without additional MC

MEROPENEM VS CONTROLS				
Variables	Total subjects n=264	Meropenem-sparing regimen n=168	Meropenem-containing regimen n=96	p-value
Admission year, n (%)				<0.0001
2003	1/264 (0.4)	1/168 (0.6)	0/96 (0.0)	
2005	2/164 (0.8)	2/168 (1.2)	0/96 (0.0)	
2007	10/264 (3.8)	10/168 (6.0)	0/96 (0.0)	
2008	17/264 (6.4)	15/168 (8.9)	2/96 (2.1)	
2009	21/264 (8.0)	14/168 (8.3)	7/96 (7.3)	
2010	32/264 (12.1)	17/168 (10.1)	15/96 (15.6)	
2011	48/264 (18.2)	22/168 (13.1)	26/96 (27.1)	
2012	27/264 (10.2)	18/168 (10.7)	9/96 (9.4)	
2013	46/264 (13.0)	40/168 (23.8)	6/96 (6.3)	
2014	51/264 (19.3)	26/168 (15.5)	25/96 (26.0)	
2015	6/264 (66.7)	3/168 (1.8)	6/96 (6.3)	
Age at the admission years, median (IQR)	33 (26-43)	32 (26-44)	34 (26-43)	0.79
Males, n (%)	137/263 (52.1)	83/167 (49.7)	54/96 (56.3)	0.31
Country of birth, n (%)				<0.0001
Africa	35/264 (13.39	30/168 (17.9)	5/96 (5.2)	
Asia	36/264 (13.6)	33/168 (19.6)	3/96 (3.1)	
Europe	168/264 (63.6)	96/168 (57.1)	72/96 (75.0)	
Others	25/264 (9.5)	9/168 (5.4)	16/96 (16.7)	
Migrant, n (%)	202/264 (76.5)	129/168 (76.8)	73/96 (76.0)	0.89
HIV test offered, n (%)	249/260 (95.8)	161/166 (97.0)	88/94 (93.6)	0.20
HIV-positive, n (%)	13/251 (5.2)	5/162 (3.1)	8/89 (9.0)	0.04
Exposure to antiretroviral therapy (ART), n (%)	11/13 (84.6)	5/5(100.0)	6/8 (75.0)	0.22
Previous exposure to anti-TB therapy, n (%)	125/262 (47.7)	59/167 (35.3)	66/95 (52.8)	<0.0001
Number of times treated >1 month, median (IQR)	1 (0–3)	1 (0–2)	2 (1–4)	<0.0001
Surgical treatment, n (%)	21/257 (8.2)	7/165 (4.2)	14/92 (15.2)	0.002

MDR-TB: multidrug-resistant tuberculosis; XDR-TB: extensively drug-resistant tuberculosis; OBR: optimized background regimen. Denominators were different among the selected variables because of missing data.

Table 4.1 continues on next page.

Table 4.1: ***Continued***

MEROPENEM/CLAVULANATE VS CONTROLS				
Variables	Total subjects	Meropenem-/ clavulanate-sparing regimen	Meropenem-/ clavulanate-containing regimen	p-value
Prior treatment outcome, n (%)				
Failed	72/122 (59.0)	23/60 (38.3)	49/62 (79.0)	<0.0001
Default	6/122 (4.9)	1/60 (1.7)	5/62 (8.1)	
Completed	7/122 (5.7)	5/60 (8.3)	2/62 (3.2)	
Cured	7/122 (5.7)	2/60 (3.3)	5/62 (8.1)	
Transferred out	1/122 (0.8)	1/60 (1.7)	0/62 (0.0)	
Relapse	1/122 (0.8)	0/60 (0.0)	1/62 (1.6)	
Unknown	28/122 (23.0)	28/60 (46./9	0/62 (0.0)	
Form, n (%)				
New	139/247 (56.3)	107/151 (70.9)	32/96 (23.0)	<0.0001
Relapse	32/247 (13.0)	19/151 (12.6)	13/96 (13.5)	
Chronic	15/247 (6.1)	0/151 (0.09	15/96 (15.6)	
Failure	61/247 (24.7)	25/151 (16.6)	36/96 (37.5)	
Pulmonary TB, n (%)	241/264 (91.3)	148/168 (88.1)	93/96 (96.9)	0.015
Extra-pulmonary TB, n (%)	44/264 (16.7)	30/168 (17.9)	14/96 (14.6)	0.49
Radiological findings, n (%)				
Cavitary lesions	38/238 (16.0)	22/145 (15.2)	16/93 (17.2)	0.001
Bilateral pulmonary involvement with cavitary lesions	96/238 (40.3)	46/145 (31.7)	50/93 (53.8)	
Bilateral pulmonary involvement	50/238 (21.0)	34/145 (23.5)	16/93 (32.0)	
Noncavitary nonbilateral pulmonary involvement	54/238 (22.7)	43/145 (29.7)	11/93 (11.8)	
Sputum smear positive, n (%)	182/250 (72.8)	97/154 (63.0)	85/96 (88.5)	<0.0001
Sputum culture positive, n (%)	249/251 (99.2)	153/155 (98.7)	96/96 (100.0)	0.53
Streptomycin resistance, n (%)	198/240 (82.5)	122/160 (76.3)	76/80 (95.0)	<0.0001
Isoniazid resistance, n (%)	264/264 (100.0)	168/168 (100.0)	96/96 (100.0)	-
Rifampicin resistance, n (%)	262/264 (99.2)	167/168 (99.4)	95/96 (99.0)	0.69
Ethambutol resistance, n (%)	172/259 (66.4)	92/164 (56.1)	80/95 (84.2)	<0.0001
Pyrazinamide resistance, n (%)	157/235 (66.8)	73/141 (51.8)	84/94 (89.4)	<0.0001
Fluoroquinolones resistance, n (%)	73/255 (28.6)	27/161 (16.8)	46/94 (48.9)	<0.0001
Ethionamide resistance, n (%)	63/159 (39.69	63/159 (39.6)	63/86 (73.3)	<0.0001
Cycloserine resistance, n (%)	39/186 (21.0)	24/111 (21.6)	15/75 (20.0)	0.79
Amikacin resistance, n (%)	61/244 (25.0)	21/162 (13.0)	40/82 (48.8)	<0.0001
PAS resistance, n (%)	32/104 (30.8)	9/57 (15.8)	23/47 (48.9)	<0.0001
Capreomycin resistance, n (%)	55/207 (26.6)	17/126 (13.5)	38/81 (46.9)	<0.0001
Kanamicin resistance, n (%)	53/163 (32.5)	16/88 (18.2)	37/75 (49.3)	<0.0001
Linezolid resistance, n (%)	5/172 (2.9)	1/97 (1.0)	4/75 (5.3)	0.10
Rifabutin, resistance n (%)	108/137 (78.8)	83/111 (74.8)	25/26 (96.2)	0.02
Others resistance, n (%)	9/27 (33.3)	3/16 (18.8)	6/11 (54.6)	0.10
Number of antibiotic resistances, median (IQR)	6 (4–8)	5 (4–6)	8 (6–9)	<0.0001

Table 4.1 continues on next page.

Table 4.1: ***Continued***

MEROPENEM/CLAVULANATE VS CONTROLS				
Variables	Total subjects	Meropenem-/clavulanate-sparing regimen	Meropenem-/clavulanate-containing regimen	p-value
Length of hospital stay days, median (IQR)	100 (63–175)	99 (78–181)	101 (61–172)	0.47
Months of treatment after MDR-TB diagnosis, median (IQR)	18 (14–20)	18 (12–20)	18 (18–22)	0.09
XDR, n (%)	57/264 (21.6)	10/168 (6.0)	47/96 (49.0)	<0.0001
Moxifloxacin, n (%)	210/254 (82.7)	133/159 (83.7)	77/95 (81.1)	0.60
Levofloxacin, n (%)	35/261 (13.4)	26/165 (15.8)	9/96 (9.4)	0.15
Linezolid, n (%)	74/188 (39.4)	24/98 (24.5)	50/90 (55.6)	<0.0001
Delamanid, n (%)	1/239 (0.4)	0/144 (0.0)	1/95 (1.1)	0.40
Bedaquiline, n (%)	11/239 (4.6)	2/144 (1.4)	9/95 (9.5)	0.008

TB: tuberculosis; IQR: interquartile range; XDR-TB: extensively drug-resistant tuberculosis. Denominators were different among the selected variables because of missing data.

Most cases (91.3%) were affected by a pulmonary TB, with a percentage of sputum smear and culture confirmation of 72.8 and 99.2%, respectively. Almost half of the cases (47.7%) were previously treated (in the majority of the cases for drug-susceptible TB, according to the medical history), and the commonest previous treatment outcome was failure (59.0%), and 8.2% underwent surgery.

Patients treated with MC-containing regimen showed a greater drug-resistance profile than those exposed to a MC-sparing regimen: in the former group XDR-TB was more frequent (49% vs 6.0%; $p<0.0001$), and the median (IQR) number of antibiotic resistances was higher [8 (6-9) vs. 5 (4–6)].

Patients were treated with a MC-containing regimen for a median of 85 (49–156) days (Table 4.2). No statistically significant differences in terms of effectiveness indicators were observed in the overall MDR-TB cohort and in the subgroups with and without the XDR-TB patients; in particular, sputum smear and culture conversion rates were similar in XDR-TB patients exposed to MC-containing regimens (88.0% vs., 100.0%, $p=1.00$, and 88.0% vs. 100.0%; $p=1.00$, respectively) (Table 4.3 and Figure 4.1).

A sub-analysis performed after stratifying all MDR-TB cases for resistance to <6 or ≥6 drugs (median number of drug resistances in the entire cohort) did not identify any statistically significant differences in sputum smear and culture conversion rates and treatment success rates between the two arms, with the only exception of the higher treatment success in those with <6 drug resistances and treated with a MC-sparing regimen.

Only 6 cases reported adverse events that could be attributable to MC, and 4 of them restarted the drug after its interruption (Table 4.2).

Table 4.2: Safety and tolerability of meropenem/clavulanate-containing regimens

MEROPENEM VS CONTROLS – Safety				
Variables	Total subjects	Meropenem-/clavulanate-sparing regimen	Meropenem-/clavulanate-containing regimen	p-value
Interruption of Linezolid, n (%)	36/159 (22.6)	13/69 (18.8)	23/90 (25.6)	0.32
Interruption of linezolid due to adverse events (AEs), n (%)	25/139 (18.0)	11/57 (19.3)	14/82 (17.1)	0.74
AEs presumably due to linezolid, n (%)	50/145 (34.5)	13/56 (23.2)	37/89 (41.6)	0.02
Anaemia, n (%)	28/166 (16.9)	8/74 (10.8)	20/92 (21.7)	0.06
Leukopaenia, n (%)	9/169 (5.3)	5/78 (6.4)	4/91 (4.4)	0.56
Piastrinopenia, n (%)	11/148 (7.4)	0/57 (0.0)	11/91 (12.1)	0.007
Peripheral neuropathy, n (%)	41/161 (25.5)	12/70 (17.1)	29/91 (31.9)	0.03
Gastro-intestinal disorder, n (%)	22/151 (14.6)	14/60 (23.3)	8/91 (8.8)	0.013
Optic neuritis, n (%)	1/173 (0.6)	1/82 (1.2)	0/91 (0.0)	0.29
Reversible AEs, n (%)	69/110 (62.7)	25/47 (53.2)	44/63 (69.8)	0.07
Linezolid restarted if interrupted, n (%)	24/88 (27.3)	5/45 (11.1)	19/43 (44.2)	<0.0001
Total linezolid exposure, median (IQR)	143 (51–540)	105 (0–458)	173 (78–540)	0.006
Interruption of meropenem, n (%)	-	-	52/94 (55.3)	-
Interruption of meropenem due to AEs, n (%)	-	-	8/94 (8.5)	-
AEs presumably due to meropenem, n (%)	-	-	6/93 (6.5)	-
Meropenem restarted if interrupted, n (%)	-	-	4/8 (50)	-
Total meropenem exposure, median (IQR)	-	-	85 (49–156)	-

IQR: interquartile range. Denominators were different among the selected variables because of missing data.

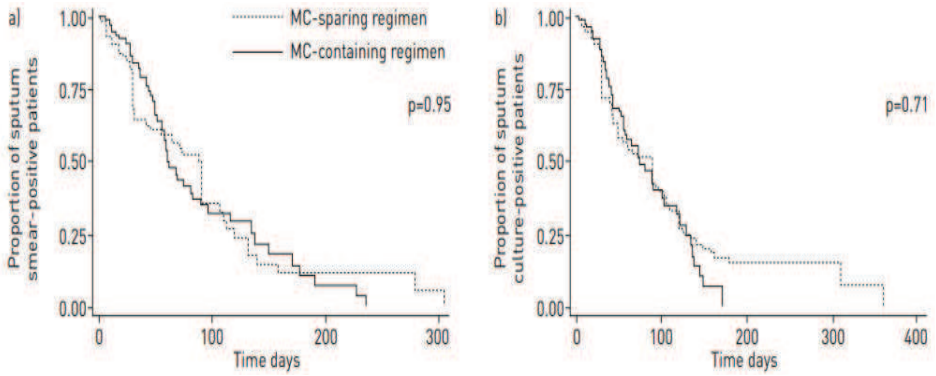


Figure 4.1: Sputum-smear (a) and culture (b) conversion in MDR-TB patients exposed and not exposed to meropenem/clavulanate-containing regimens.

Table 4.3: Treatment outcomes for patients exposed and not exposed to meropenem/clavulanate-containing regimens

MEROPENEM VS CONTROLS – Clinical findings				
Variables	Total subjects	Meropenem-sparing regimen	Meropenen-containing regimen	p-value
Sputum smear conversion, n (%)	155/160 (96.9)	100/102 (98.0)	55/58 (94.8)	0.35
Sputum smear conversion at 30 days of treatment, n (%)	128/227 (56.4)	91/133 (68.4)	37/94 (39.4)	<0.0001
Sputum smear conversion at 60 days of treatment, n (%)	148/208 (71.2)	89/117 (76.1)	59/91 (64.8)	0.08
Sputum smear conversion at 90 days of treatment, n (%)	169/201 (84.1)	93/111 (83.8)	76/90 (84.4)	0.90
Sputum smear conversion in patients with <6 resistances, n (%)	65/66 (98.5)	56/57 (98.3)	9/9 (100.0)	1.00
Sputum smear conversion in patients with ≥6 resistances, n (%)	90/94 (95.7)	44/45 (97.8)	46/49 (93.9)	0.62
Sputum smear conversion in MDR-TB patients, n (%)	126/128 (98.4)	93/95 (97.9)	33/33 (100.0)	1.00
Sputum smear conversion in XDR-TB patients, n (%)	29/32 (90.6)	7/7 (100.0)	22/25 (88.0)	1.00
Sputum smear conversion in MDR-TB patients without resistance to fluoroquinolones, n (%)	142/145 (97.9)	107/110 (97.3)	35/35 (100.0)	1.00
Sputum smear conversion in MDR-TB patients with resistance to fluoroquinolones, n (%)	29/30 (96.7)	17/18 (94.4)	12/12 (100.0)	1.00
Sputum culture conversion, n (%)	156/159 (98.1)	101/101 (100.0)	55/58 (94.8)	0.05
Sputum culture conversion at 30 days of treatment, n (%)	100/210 (47.6)	70/116 (60.3)	30/94 (31.9)	<0.0001
Sputum culture conversion at 60 days of treatment, n (%)	118/186 (63.4)	59/93 (63.4)	59/93 (63.4)	1.00
Sputum culture conversion at 90 days of treatment, n (%)	132/180 (73.3)	60/89 (67.4)	72/91 (79.1)	0.08
Sputum culture conversion in patients with <6 resistances, n (%)	66/66 (100.0)	57/57 (100.0)	9/9 (100.0)	1.00
Sputum culture conversion in patients with ≥6 resistances, n (%)	90/93 (96.8)	44/44 (100.0)	46/49 (93.9)	0.24
Sputum culture conversion in MDR-TB patients, n (%)	127/127 (100.0)	94/94 (100.0)	33/33(100.0)	1.00
Sputum culture conversion in XDR-TB patients, n (%)	29/32 (90.6)	7/7 (100.0)	22/25 (88.0)	1.00
Sputum culture conversion in MDR-TB patients without resistance to fluoroquinolones, n (%)	140/141 (99.3)	105/106 (99.1)	35/35 (100.0)	1.00
Sputum culture conversion in MDR-TB patients with resistance to fluoroquinolones, n (%)	29/30 (96.7)	17/18 (94.4)	12/12 (100.0)	1.00
Days from start of anti-TB therapy to sputum smear conversion, median (IQR)	30 (7–61)	30 (0–56)	45 (28–68)	0.0002

Table 4.3 continues on next page.

Table 4.3: ***Continued***

MEROPENEM VS CONTROLS – Clinical findings				
Variables	Total subjects	Meropenem-sparing regimen	Meropenen-containing regimen	p-value
Days from start of anti-TB therapy to culture conversion, median (IQR)	42 (29–90)	42 (30–90)	44 (28–75)	0.81
Treatment outcome, n (%)				0.001
Cured	89/264 (33.7)	67/168 (39.9)	22/96 (22.9)	
Treatment completed	81/264 (30.7)	48/168 (28.6)	33/96 (34.4)	
Still on treatment	54/264 (20.5)	30/168 (17.9)	24/96 (25.0)	
Died	14/264 (5.3)	3/168 (1.8)	11/96 (11.5)	
Default	21/264 (8.0)	16/168 (9.5)	5/96 (5.2)	
Transferred out	5/264 (1.9)	4/168 (2.4)	1/96 (1.0)	
Treatment success, n (%)	170/264 (64.4)	115/168 (68.5)	55/96 (57.3)	0.07
Treatment success in patients with <6 resistances, n (%)	76/91 (83.5)	67/77 (87.0)	9/14 (64.3)	0.035
Treatment success in patients with ≥6 resistances, n (%)	92/111 (82.9)	46/54 (85.2)	46/57 (80.7)	0.53
Treatment success in MDR-TB patients, n (%)	141/207 (68.1)	108/158 (68.4)	33/49 (67.4)	0.90
Treatment success in XDR-TB patients, n (%)	29/57 (50.9)	7/10 (70.0)	22/47 (46.8)	0.30

MDR-TB: multidrug-resistant tuberculosis; XDR-TB: extensively drug-resistant tuberculosis; IQR: interquartile range.

Discussion

Aim of our study was to evaluate the therapeutic contribution of MC when added to a background regimen (as per WHO guidelines) in terms of effectiveness, safety, and tolerability in treating MDR- and XDR-TB cases.

The results of our study demonstrates that MC-containing and -sparing regimens achieve similar sputum smear and culture conversion rates in XDR-TB cases. No statistically significant differences in terms of treatment outcomes were observed between the patients with and without MC-containing regimen, in spite of the fact that the former had a more severe form of disease and a larger number of drug resistances. Furthermore, the safety profile of MC (previously demonstrated in the treatment of other bacterial diseases) was confirmed, and only 2 patients did not continue the treatment with MC.

This is, to our knowledge, the first largest study (sample size >90) on MC administered to TB patients in the scientific literature. Among the strengths of the study we mention the large size of the entire cohort and the detailed information collected from all 5 centres and 3 countries in Europe and Latin America.

However, the study shows the following limitations, which are in-built in its observational, retrospective design. 1) Hhaving not been planned prospectively, the computation of a primary hypothesis-based sample size was not allowed. 2) Given each regimen (as per WHO guidelines) consisted of a cocktail of drugs, it is difficult to attribute a specific effect to a specific drug (MC in this case). 3) No randomization and blindness procedures were performed. 4) As expected, the patients enrolled in the MC-containing arm were significantly more complicated in terms of drug-resistance patterns, while most of the demographic, epidemiological, and clinical variables did not differ significantly. In this respect, the non-different result in terms of outcomes and bacteriological conversions observed in MDR- and XDR-TB cases might imply that MC could be active. This finding needs to be confirmed by controlled clinical trials which will remove the 'background noise' produced by the observational design. 5) As no standard DST for MC was available, some isolates may have been resistant to the drug. The evidence provided by this study allows greater understanding on the role of carbapenems, and confirms the results of previous studies.[29,30] MC is safe and its activity appears promising, although probably not as active as other repurposed drugs (e.g. linezolid[22-28]).

Furthermore, it should be highlighted that MC is expensive if compared with other antibiotics and is not available in all countries, particularly in geographical areas with a high M/XDR-TB burden and limited economic resources.

We note that treatment success in the cohort of the XDR-TB patients treated with MC was higher than that achieved in the largest observational cohort available in the literature (46.8 vs. 40.0%).[3,4] It will be interesting to compare the results of this study with an ongoing one (by the same international group) on imipenem, which is cheaper and more widely available.

As the future role of carbapenems in the treatment of MDR- and XDR-TB needs further discussion,[9,41] the evidence provided by this observational study offers new information to clinicians treating severely resistant TB cases (e.g., those with resistances to 6 drugs or more or with intolerance to drugs) and lacking the minimum number of active drugs necessary to design an effective regimen.[3,4] For this reason, 12 of the patients treated with MC were prescribed bedaquiline (n=11) or delamanid (n=1). For other drugs which are already in use (sulphonamides[42,43] and mefloquine among others[44] even less evidence is presently available.

Although combination of MC with delamanid and bedaquiline is potentially useful to avoid rapid resistance development to the new compounds, some concerns have been raised on the QTc prolongation and related cardiotoxicity. Fortunately, no cases were detected in our study. This toxicity might be further enhanced by other second-line drugs like fluoroquinolones or clofazimine.[45]

Although observational studies show some methodological shortcomings, they could offer rapid orientation on the drug effectiveness and safety in order to better inform future clinical trials. In the case of linezolid the observational evidence was confirmed by that generated by a clinical trial.[26]

Results of a phase IIa study evaluating early bactericidal activity of MC (NCT02349841) are expected soon and may confirm our results. Also, oral carbapenems currently under evaluation (like faropenem, NCT02349841 and NCT02381470) might shed new light on the use of carbapenems for the treatment of MDR/XDR-TB.

Moreover, the results suggest that MC can improve the outcome in MDR- and XDR-TB, although further studies correlating resistance testing for carbapenems with outcomes are necessary.

Phenotypic/genotyping resistance testing for MC susceptibility may assist clinicians in identifying patients who may benefit from treatment of this drug.

MDR-TB is a global public health priority and challenge; the rapid implementation of new clinical trials with repurposed drugs is an important component towards TB Elimination that needs to be addressed.[46]

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Chapter 5

Comparison of effectiveness and safety of imipenem/clavulanate added to an optimised background regimen (OBR) versus OBR controls regimens in the treatment of multidrug and extensively drug-resistant tuberculosis

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Summary

Eighty-four imipenem/clavulanate-treated cases were retrospectively compared with 168 controls undergoing optimised background regimen treatment. Cases were more severe and achieved non-different or lower sputum smear/culture conversion and treatment success rates than controls (79.7% vs. 98.0%, $p<0.0001$; 71.9% vs. 100.0%; $p<0.0001$, and 59.7% vs. 85.8%; $p<0.0001$, respectively).

TO THE EDITOR — Treating multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant (XDR)-TB patients is long, expensive, and complicated, particularly when four active drugs recommended to design an effective regimen are missing.[1-5] New drugs (i.e., bedaquiline and delamanid[6,7]) and a few re-purposed ones, linezolid[8,9] and carbapenems,[10-12] are attracting interest. To date the largest clinical study evaluating imipenem/clavulanate (IC) to treat MDR-TB included 10 cases.[12]

The aim of our observational study was to compare the therapeutic contribution (effectiveness, safety, and tolerability profile) of IC added to an optimised background regimen (OBR) designed per World Health Organization guidelines[4] vs. an OBR control group to treat MDR-/XDR-TB cases. Eighty-four consecutive patients treated with IC-containing regimens were compared with 168 controls recruited by the International Carbapenems Study Group in 21 centres and 8 countries located in Europe and Latin America[10,11] between 2003 and 2015. Data from culture-confirmed MDR-TB patients with Mycobacterial strains resistant to at least isoniazid and rifampicin, were analysed.

An OBR regimen was administered following DST carried out by externally quality-assured laboratories.[10,11] Physicians prescribed anti-TB drugs without any compelling criteria of experimental protocols and, consequently, blinding or randomized methods were not followed. Imipenem was administered at a dose of 500 mg four times a day for a median (IQR) of 187 (60–428) days.

IC-treated cases showed higher previous exposure [median (IQR)] to anti-TB drugs >1 month [2 (1-3) vs. 1 (0–2)] and number of resistances [8 (7–8) vs. 5 (4–6)] than OBR-controls. Furthermore, cases exposed to IC showed more resistance to fluoroquinolones (79.0% vs. 16.8%; $p<0.0001$), amikacin (50.0% vs. 13.0%; $p<0.0001$), kanamycin (75.8% vs. 18.2%; $p<0.0001$), capreomycin (63.9.% vs. 13.5%; $p<0.0001$), and higher XDR-TB prevalence (67.9% vs. 6.0%; $p<0.0001$) than OBR-controls.

The median time to sputum smear conversion was similar between IC-treated patients and controls [30 (30–60) days vs. 30 (0–56) days; $p<0.001$], whereas time to culture conversion was higher among cases than OBR-controls, although not statistically significant [60 (30–90) days vs. 42 (30–90) days; $p=0.08$] (Figure 5.1). Sputum smear and culture conversion rates were lower among cases than OBR-controls (79.7% vs. 98.0%, $p<0.0001$, and 71.9% vs. 100.0%; $p<0.0001$, respectively) as were success rates (59.7% vs. 85.8%; $p<0.0001$), while death (17.9% vs. 1.8%; $p<0.0001$) and failure rates (6.0% vs 0.0%; $p<0.0001$) were higher. Adverse events (minor) due to IC were reported in only 5.4%.

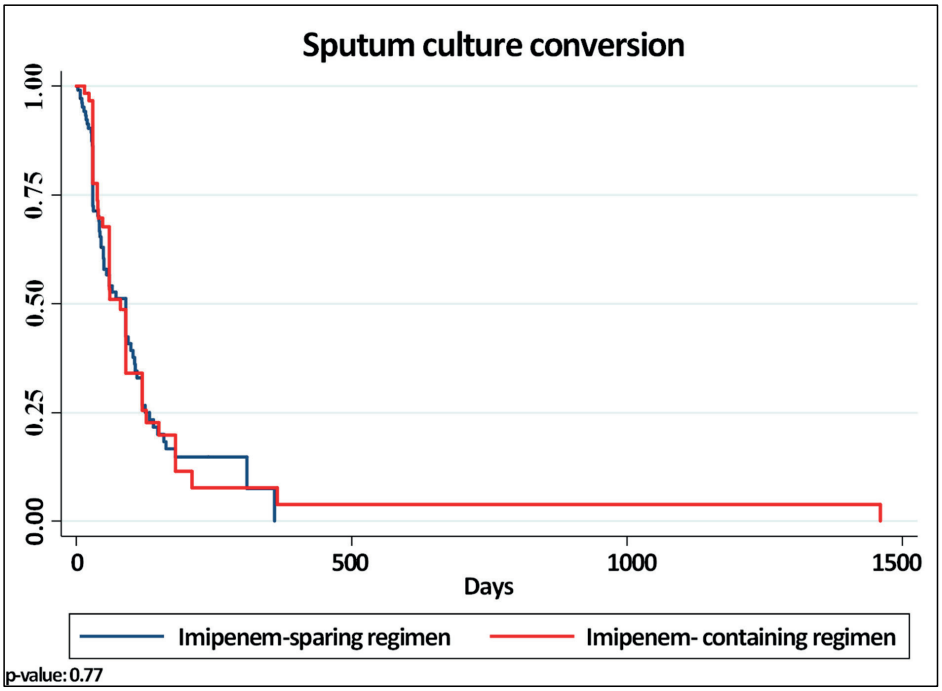


Figure 5.1: Culture conversion in multidrug-resistant patients exposed and not exposed to imipenem/clavulanate.

Findings show that IC-containing regimens achieved non-different or worse results than IC-sparing ones. Perhaps the severity of IC-treated cases, in the absence of alternatives favoured the administration of a carbapenem. Therefore, selection bias related to the retrospective, observational nature of the study cannot be excluded. Interestingly, the success rates among IC-treated is similar to that achieved in other major international MDR-TB cohorts, confirming IC might have a role in MDR-TB treatment.[1,2,12]

This is, to our knowledge, the first large study describing effectiveness, safety, and tolerability of IC-containing regimens while comparing its clinical performances with a control group.

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Chapter 6

Renal Fanconi Syndrome with meropenem-containing regimen in drug-resistant tuberculosis

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We read with great interest the correspondence by M. Abadie et al.,[1] describing the case of an extensively drug-resistant tuberculosis (XDR-TB) patient developing renal Fanconi syndrome while receiving a meropenem/amoxicillin-clavulanate-containing regimen.

The International Carbapenem Study Group centres collected data on 96 patients treated with meropenem/clavulanate and 84 patients with imipenem/clavulanate; carbapenem and beta lactam/lactamase inhibitor combinations were well tolerated, no cases of Fanconi syndrome were encountered.[2,3] Other groups have also published their experience and there were no cases of Fanconi syndrome (Table 5.1).[4]

Meropenem dosing and duration were heterogeneous in our study group; the majority of patients were administered meropenem for a median of 85 (range: 49–156) days, particularly during the intensive phase or until their sputum culture conversion.[2] Only the Belgian team prescribed a higher dosage of meropenem for more extended periods[5] (Table 5.1[2,3,5-11]). Meropenem/amoxicillin-clavulanate, given its bactericidal qualities, appears ideally placed in the intensive phase until sputum culture conversion occurs.

If required ertapenem/clavulanate may be used in the continuation phase.[10]

Several drugs are known to cause proximal renal tubular acidosis (RTA) with Fanconi syndrome. It can be caused by several drugs including aminoglycosides, rifampicin, cisplatin, and tenofovir dipivoxil fumarate. Generally, RTA is reversible removing the offending drug. Meropenem and amoxicillin/clavulanate are not typically given for prolonged periods or in combination. In normal circumstances, Fanconi syndrome has not been regularly reported for either of the two drugs and could be considered rare.

The occurrence of this rare adverse event, related to a drug with well documented toxicity, and the paucity of limited published evidence on their safety and tolerability is an advocacy for active drug safety monitoring (aDSM) of anti TB medications.[12-14] Data collection is essential for clinicians and drug advisory bodies to ensure patient safety. Further attention with regards to formulations and preparation of meropenem, as well as its subsequent storage temperature, is also worth considering.

Table 5.1: Studies available in the literature reporting on carbapenems for the treatment of drug-resistant tuberculosis

Study and reference	XDR-TB cases out of the total number of cases studied (%)	Control group	Adverse reactions number (%)	Carbapenem and dosage
Chambers et al. (2005)[6]	2/10 (20.0)	No	Not done	Imipenem 1 g bid
Palmero et al. (2015)[7]	4/10 (40.0)	No	0/10 (0.0)	Meropenem 2 g tid, then 1 g tid
De Lorenzo et al. (2013)[8]	9/37 (24.3)	Yes	5/37 (13.5)	Meropenem 1 g tid
Van Rijn et al. (2016)[9]	N.D*	No	2/18 (11.1)	Ertapenem 1 g qd
Tiberi et al. (2016)[10]	2/5 (40.0)	No	0/5 (0.0)	Ertapenem 1 g qd
*Tiberi et al. (2016)[2]	47/96 (49.0)	Yes	6/93 (6.5)	Meropenem 1 g tid
Tiberi et al. (2016)[11]	57/84 (67.9)	Yes	3/56 (5.4)	Imipenem 500 mg qid
* Tiberi et al. (2016)[3]	Imipenem 57/84 (67.9) Meropenem 47/96 (49.0)	No	Imipenem 3/56 (5.4) Meropenem 6/93 (6.5)	Imipenem 500 mg qid Meropenem 1 g tid
Payen et al. (2018)[5]	15/18 (83.3)**	No	0/18 (0.0)	Meropenem 2 g tid, then 2 g bid

qd: once a day; bid: twice a day; tid: thrice a day; qid: quarter: four times a day; ND: not declared; XDR-TB: extensively drug-resistant tuberculosis. * Cohorts enrolled in the studies n.6 and n.8. ** Children were included in these studies.

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Chapter 7

Pulmonary tuberculosis in intensive care setting, with a focus on the use of severity scores, a multinational collaborative systematic review

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Summary

Background and aim: Tuberculosis (TB) is associated with a high mortality in the intensive care unit (ICU), especially in subjects with Acute Respiratory Distress Syndrome (ARDS) requiring mechanical ventilation. Despite its global burden on morbidity and mortality, TB is an uncommon cause of ICU admission, however mortality is disproportionate to the advances in diagnosis and treatment made. Herein we report a systematic review of published studies.

Methods: Our literature search was conducted to identify studies on outcomes of individuals with TB admitted to ICU. We report and review in-hospital mortality, predictors of poorer outcomes, usefulness of severity scoring systems and potential benefits of intravenous antibiotics. Searches from Pubmed, Embase, Cochrane and Medline were conducted from inception to March 2020. Only literature in English was included.

Results: Out of 529 potentially relevant articles, 17 were included. Mortality across all studies ranged from 29–95% with an average of 52.9%. All severity scores underestimated average mortality. The most common indication for ICU admission was acute respiratory failure (36.3%). Negative predictors of outcome included hospital acquired infections, need of mechanical ventilation and vasopressors, delay in initiation of anti-TB treatment, more than one organ failure and a higher severity score. Low income, high incidence countries showed a 23.4% higher mortality rate compared to high income, low TB incidence countries.

Conclusion: Mortality in individuals with TB admitted to ICU is high. Earlier detection and treatment initiation is needed.

Introduction

Tuberculosis (TB) was within the top ten causes of death and second cause of death from a single infectious agent worldwide in 2020.[1-4] The aim of treatment is to reduce the incidence of resistance and achieve full bacterial clearance, thereby limiting the risk of transmission.[5,6] Success of drug susceptible TB under trial conditions is up to 95% in non-critical subjects; this success is underpinned by adequate concentrations of these drugs in the blood.[7]

Although TB most commonly manifests sub-acutely or chronically, some individuals especially those with extensive disease may progress rapidly, requiring admission to intensive care unit (ICU). Up to 3% of all patients with TB require ICU admission, a high proportion considering the availability of curative treatment.[8] The most common indication for ICU admission is respiratory failure and acute respiratory distress syndrome (ARDS).[9-11] The mortality for TB patients admitted to ICU is extremely high, more than any other cause of respiratory failure including pneumonia.[12] Reported mortality rates are variable across studies, and can range from 24% to 81% in individuals requiring mechanical ventilation.[13] The mortality for ARDS secondary due to TB has not changed significantly over time, despite advances in new treatment regimens and ventlilatory strategies in ICU. The heterogeneity of disease presentation and the difficulty in diagnosis remain a challenge. Co-morbidities including HIV, immunosuppressive disorders and diabetes increase the risk of complications in patients with TB.[9] Poor prognostic indicators include high Acute Physiology And Chronic Health Evaluation II (APACHE II) or Simplified Acute Physiology Score (SAPS) II scores, nosocomial infections, sepsis and delayed start of anti TB treatment.[14] The full extent of the association of TB with Covid-19 and the risk of admission to ICU and the need for mechanical ventilation is currently not known.[15-18]

Delays in diagnosis and treatment of pulmonary TB are principal causes of death, especially in patients with acute respiratory failure.[11,19,20] Early diagnosis and start of effective treatment is needed to prevent ICU admission and complications.[9] It is imperative that the absorption of anti-TB treatment is maximised; a challenge in the critically ill individual. Deranged physiological functioning and poor gastric absorption can lead to sub-therapeutic drug levels.[21] Intravenous antibiotics may overcome these obstacles. Despite the bioavailability of parenteral routes, the use of intravenous antimicrobials is seldom used in TB. If intravenous rifampicin, was more widely available, it may negate the need for more toxic regimens.

Severity scoring systems such as APACHE II have been proven to predict mortality in individuals admitted to ICU.[22] This may not be the case for individuals with TB related ARDS and septic shock, as some studies have suggested they consistently underestimate mortality in these groups.[23,24] The low prevalence of TB in ICU is a further challenge. In published studies, small sample sizes limit the potential generalisation of results.[25] Further research and studies with larger patient groups are needed.

This review aims to identify factors affecting poor outcomes and mortality of individuals with pulmonary TB admitted to ICU. Further objectives include identifying factors leading to TB-related complications, the relevance of ICU severity scores and the role of using first line intravenous anti-TB drugs in critically ill subjects. We hypothesise that identifying predictors of poor outcomes in TB patients admitted to ICU can contribute to risk stratification and personalised treatment.

Methods

Search strategy

To avoid any influence of the effects of pandemic on recent publications,[26] Pubmed, EMBASE, Cochrane and Medline databases were searched from inception until March 2020. Keywords included: ("Outcome*" or "mortality" or "impact" or "recovery" or "effect*") AND ("Mycobacterium tuberculosis" or "tuberculosis" or "TB" or 'MTB") AND ("intensive care unit*" or "intensive treatment unit*" or "critical care" or "CCU" or "ARDS" or "Acute respiratory distress syndrome" or "mechanical ventilation" or "respiratory failure") and ("scor*" or "severity" or "APACHE" or "APACHEII" or "GCS" or "SOFA" or "SAPS" or "Charlson"), "Intravenous" or "antibiotic*" or "Rifampin" or "Isoniazid" or "ethambutol" or "Pyrazinamide".

Study selection

Published studies were included if they reported on outcomes of cohorts of patients with pulmonary TB admitted to ICU Studies involving, individuals <18 years and those involving <10 patients were excluded. Conference abstracts, posters, patient case studies and articles with no reported outcomes were excluded.

In the first stage, we screened the titles and abstracts of all citations for potentially relevant papers. In the second stage, we examined in detail the full texts of the retrieved papers.

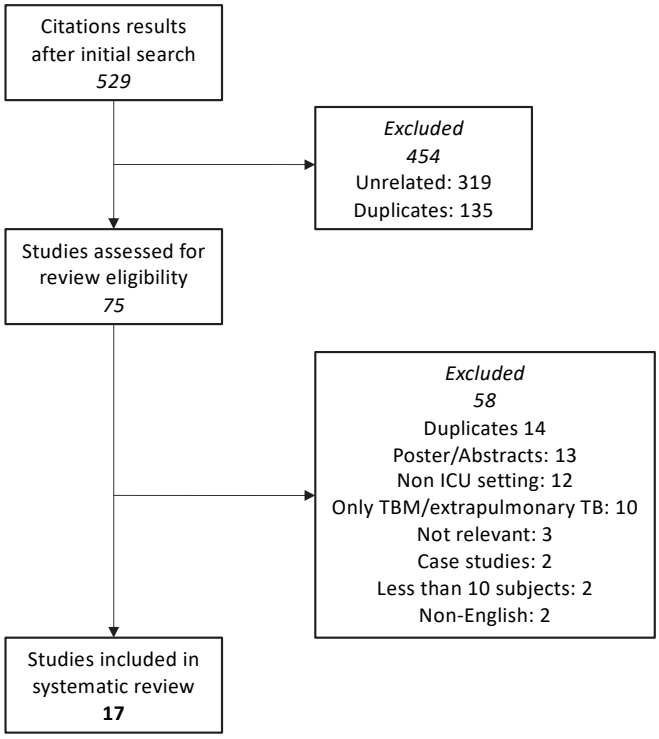


Figure 7.1: Flowchart of study selection.

Data extraction

Information on study design, setting, population characteristics including comorbidities, reason for ICU admission as well as ICU outcomes were obtained (see Table 7.1). Factors affecting outcomes were also recorded in a separate Table 7.2, and including information on mechanical ventilation, length of hospital and ICU stay, ICU related complications were obtained. Tuberculosis related outcomes such as time to initiation of anti-TB treatment, drug susceptibility pattern, concomitant treatments, were recorded (Table 7.2). All ICU related severity scores were recorded (Table 7.3).

Table 7.1: Studies of patients with tuberculosis in the intensive care setting

Study	Country (incidence per 100,000)	Study duration	Study design	Patients n	Mean* age of patients (years)	M:F	Co-morbidities n (%)	TB diagnosis before ICU admission n (%)	Indication for ICU admission
Penner et al.[32] (1995)	Canada (6)	1984–1994	Retrospective	13	47±14.0	6:7	Alcohol abuse 6 (46.2) Malnourished 7 (53.8)	7 (53.8)	NR
Erbes et al.[14] (2006)	Germany (7)	1990–2001	Retrospective	58	44.7±17.7	36:12	Malnourished 30 (51.7) Liver damage 38 (65.5) Alcohol abuse 35 (60.3) Smoking 40 (69.0)	46 (79.3)	ARDS 47 (81.1%)
Sharma et al.[20] (2006)	India (199)	1980–2003	Retrospective	29	31.6 ±10.9	16:13	Liver damage 11 (39.3) Alcohol abuse 3 (10.3) Diabetes 2 (6.9) Pregnancy/post partum 4 (13.8)	6(19)	NR
Ryu et al.[7] (2006)	Korea (66)	1995–2005	Retrospective	32	69 (25–88)	20:12	Diabetes 4 (12.5) Tuberculosis destroyed lung 4 (12.5) Immunosuppressive therapy 5 (15.6)	6 (19)	NR
Lin et al.[43] (2009)	Taiwan (61)	2004–2005	Retrospective	59	76.9±9.8 (F) 70.8±18.9 (S)	46:13	COPD 12 (20.3) CHF 11 (18.6) DM 13 (22.0) Chronic steroid use 13 (22.0) Malignancy 12 (20.3)	NR	NR
Valade et al.[13] (2012)	France (9)	2000–2009	Retrospective	53	41 [32–52]	40:13	HIV 12 (23.6) Smoking 32 (60.4) Alcohol use 22 (41.5) IVDU 6 (11.3)	40 (75)	NR

Balkema et al.[29] (2014)	South Africa (520)	2012–2013	Prospective	83	36.5±12.9	38:45	HIV 44 (53) DM 9 (10.8) COPD 6 (7.2)	32 (38.6)	ARDS 56 (67.5)
Lanoix et al.[31] (2014)	France (9)	2000–2009	Retrospective	97	47.4 ± 14.7	77:20	HIV 40 (41.2)	NR	Sepsis 7 (7.2) ARF 42 (43.3) Neurological disorder 25 (25.8) Haemoptysis 7 (7.2)
Rollas et al.[8] (2015)	Turkey (16)	2009–2014	Retrospective	16	45 [24–74]	9:7	Immunosuppression 8 (50) Heart failure 2 (12.5)	NR	Neurological 5 (31.3) Sepsis 5 (31.3) Haemoptysis 1 (6.3) ARF 5 (31.3)
Filiz et al.[57] (2016)	Turkey (16)	2010–2013	Retrospective	35	47 [16–83]	27:8	DM 8 (22.9) Silicosis 2 (5.7)	NR	ARF 20 (57.1) Sepsis 7 (20) Massive haemoptysis 3 (8.6) Extrapulmonary TB 3 (8.6)
Kim et al.[21] (2016)	Korea (66)	2011–2014	Retrospective	41	56.3 [47–73]	35:6	Hypertension 6 (14.6) DM 5 (12.2) Liver damage 4 (9.8) Malignancies 3 (7.3)	10 (24.4)	NR
Duro et al.[46] (2017)	Portugal (24)	2007–2014	Retrospective	39	52 (37.5–62.8)	29:10	Immunodeficiency 18 (46.2) Smoking 13 (33.3) Alcohol abuse 8 (20.5) Drug addiction 9 (23.1) COPD 8 (20.5) Malnourished 10 (25.6)	39 (100)	ARF 20 (51.3) Septic shock 8 (20.5) Post surgical 5 (12.8) Post CPR 4 (10.3) LOC 2 (5.1)

Table 7.1 continues on next page.

Table 7.1: ***Continued***

Study	Country (incidence per 100,000)	Study duration	Study design	Patients n	Mean* age of patients (years)	M:F	Co-morbidities n (%)	TB diagnosis before ICU admission n (%)	Indication for ICU admission
Kim et al.[34] (2018)	Korea (66)	2005–2016	Retrospective	125	66 (57–74)	104:21	Smoking 59 (47.2) Diabetes 25 (20.0) Hypertension 31 (24.8) CHD/CVD 40 (32.0) Chronic lung disease 53 (42.4) Liver disease 8 (6.4) Chronic kidney disease 5 (4.0) Malignancy 13 (10.4)	NR	Pneumonia 73 (58) Acute exacerbation 20 (16) Haemoptysis 19 (15)
Muthu et al.[42] (2018)	India (199)	2001–2016	Retrospective	63	37.3±19	27:36	NR	55 (87.3)	NR
Tatar et al.[19] (2018)	Turkey (16)	2004–2010	Retrospective	40	55 (43–63)	33: 7	Smoking 22 (55) COPD 12 (30) Diabetes 7 (17.5) Cardiovascular disease 3 (7.5) Psychiatric disorder 3 (7.5)	7 (17.5)	ARF 40 (100)

Table 7.2: Summary of studies showing patient variables and outcomes in ICU

Study	ICU Severity score	Invasive MV n (%)	Duration of MV (d)	Duration of hospital stay (d)	Duration of ICU stay (d)	Delay in ATT (d)	DR n (%)	Additional treatment n (%)	ICU complications n (%)	In-hospital/ ICU Mortality n (%)	Predictors of fatality	Cause of death n (%)
Penner et al.[32] (1995)	APACHE II, 26±4	13 (100)	15±10	50± 35	19±12	45±33	0 (0)	Steroids, 8 (61.5%)	Sepsis, 6 (46.2) MOF, 6 (46.2) Pneumothorax 2, (15.4) DIC, 1 (7.7) ARDS, 8 (6.2)	9 (69.0)	NR	MOF 6 (46.2) RF 3 (23.1)
Erbes et al.[14] (2006)	APACHE II, 13.1±5.6	22 (37.9)	26 (1–106)	87.1 (3–340)	21.6 (3–229)	0	7 (12.1)	Steroids, 40 (68.9)	ARDS 7 (12.1) Pneumothorax 8 (13.8) ARF 7 (12.1) Sepsis 15 (25.8) MOF 2 (3/4) HAI 39 (67.2)	15 (25.9)	ARF, MV, Chronic pancreatitis, Sepsis, ARDS, Nosocomial pneumonia	NR
Sharma et al.[20] (2006)	APACHE II, 18.5±5.7	23 (79.3)	**5 (3–26)**	**14 (3–90)**	**7 (3–90)**	NR	NR	Steroids, 6 (20.7)	UTI 5 (17.2) DIC 5 (17.2) MOF 4 (13.8) Pneumothorax 1 (3.4)	12 (41.4)	APACHE II>18, hyponatremia PaO2/FiO2 ratio <108.2	NR
Ryu et al.[7] (2006)	APACHE II, **16 [8–36]**	32 (100)	9 (2–86)	**20 (4–144)**	**11 (2–18)**	**2 (1–43)**	2 (6.3)	NR	ARDS 9 (28.1) MOF 7 (21.9) HAI 9 (28.1) Sepsis 16 (50)	19 (59)	APACHE II >20, TDL, Sepsis	NR

Table 7.2 continues on next page.

Table 7.2: ***Continued***

Study	ICU Severity score	Invasive MV n (%)	Duration of MV (d)	Duration of hospital stay (d)	Duration of ICU stay (d)	Delay in ATT (d)	DR n (%)	Additional treatment n (%)	ICU complications n (%)	In-hospital/ ICU Mortality n (%)	Predictors of fatality	Cause of death n (%)
Lin et al.[43] (2009)	APACHE II, 21±6.5	59 (100)	NR	NR	NR	NR	3 (5.1)	NR	VAP 29 (49.1) ARF 6 (10.2) GI bleed 14 (25)	40 (67.8)	MOF, Nosocomial pneumonia, treatment delay >30d	NR
Valade et al.[13] (2012)	GCS, **14 [12–15]** SAPS II, **31 [22–50]**	24 (45)	6 (3–17)	NR	**6 [3–16]**	3 (0–21)	2 (3.8)	Vasopressor 15 (28)	HAI 11 (21) VAP 11 (20.8)	20 (38)	Miliary TB, MV and vasopressor requirement	Organ failure 5 (9.4) HAI/co-infection 14 (26.4) PE 1 (1.9)
Balkema et al.[29] (2014)	APACHE II, 20.7±8.3	NR	NR	NR	11.9 (1–56)	1.6 (0–17)	3 (3.6)	NR	ARDS 26 (31.3) Renal failure 31 (37.3) VAP 19 (22.9) Septic shock 23 (27.7) DIC 15 (18.1) MODS 25 (30.1) Haemoptysis 14 (16.9) CAP 38 (45.8)	49 (59)	CD4 <200 Absent lobar consolidation Higher APACHE score, ARF	NR

Lanoix et al.[31] (2014)	SAPS II, **38 [6–121]** SOFA, **4 [0–17]**	45 (46.4)	**8 [1–129]**	NR	**7 [3–15.5]**	NR	8 (8.25)	Steroids 32 (33) Vasopressor 36 (37.1)	VAP 18 (40)	32 (33.3)	Higher SAPS II/SOFA score, 2+ infections, MV, ARDS, RRT Vasopressor support, Low GCS Lymphocytopenia Hypoproteinaemia	VAP 7 (7.2)
Rollas et al.[8] (2015)	APACHE II, **21.5 (6–36)** SOFA, **6 (1–12)** GCS, 11 **(3–15)**	10 (62.5)	**7 (3–45)**	**41 (6–122)**	**10.5 (5–122)**	1 (0–20)	1 (6.3)	NR	HAI 8 (50)	7 (43.8)	Sepsis, MV requirement, HAI, higher APACHE II	Septic shock 5 (31.3) ARF 2 (28.6)
Filiz et al.[57] (2016)	APACHE II, **18 (7–32)** SOFA, **6 (1–14)**	24 (68.6)	NR	NR	NR	NR	10 (28.6)	NR	Shock 19 (54.3) MOF 17 (48.6) ARF 13 (37.1)	20 (57.1)	Shock, MOF, MV, DR	NR
Kim et al.[21] (2016)	Charlson, 0.76±1.28 APACHE II, 20±6.7 SOFA, **7 (4–9)**	41 (100)	**6.3 [3–14]**	**13.2 [7–28]**	**7.8 [3–17]**	1	4 (9.8)	NR	ARDS 19 (46.3) VAP 15 (36.6) Sepsis 30 (73.2) Shock 38 (92.7) AKI, 12 (29.3) MOF, 27 (65.9)	39 (95.1)	NR	Hypoxemia 9 (23.1) Septic shock 16 (41.0) MOF 14 (35.9)

Table 7.2 continues on next page.

Table 7.2: ***Continued***

Study	ICU Severity score	Invasive MV n (%)	Duration of MV (d)	Duration of hospital stay (d)	Duration of ICU stay (d)	Delay in ATT (d)	DR n (%)	Additional treatment n (%)	ICU complications n (%)	In-hospital/ ICU Mortality n (%)	Predictors of fatality	Cause of death n (%)
Duro et al.[46] (2017)	APACHE II, 26 ± 15.75 SAPS II, **55 [27.5]**	29 (74.4)	**17 [39]**	NR	NR	0 [4]	NR	Steroids 5 (12.8) Vasopressor 21 (53.8) ECMO 2 (5.1)	ARDS 7 (17.9) ARF 8 (20.5) MODS 11 (28.2) HAI 11 (28.2)	21 (53.8)	Delayed ATT >3d post ICU admission MODS/Sepsis HAI	NR
Kim et al.[34] (2018)	APACHE II **19 [15–24]** SOFA, **8 [4–11]**	125 (100)	**8 [5–17]**	**20 [12–43]**	**11 [7–18]**	NR	NR	Vasopressor 58 (46) RRT 10 (8)	NR	46 (37)	Age, vasopressor use, low PaO2/FiO2 ratio, BNP	NR
Muthu et al.[42] (2018)	APACHE II, 16.1±7.2 SOFA, 1.8±1.6	56 (88.9)	7.5±9.1	16.41.2	9.8±11.4	NR	NR	Tracheostomy 9 (14.3) Steroids 18 (28.6)	ARDS 18 (28.6) VAP 10 (15.9) Pneumothorax 4 (5.8)	28 (44.4)	Baseline APACHE and SOFA score higher,	Severe sepsis 16 (25.4) Raised ICP 7 (11.1) Hypoxemia 5 (7.9)
Tatar et al.[19] (2018)	APACHE II, **22 [15–26]**	30 (75)	**4 [2–18]**	**13 [5–27]**	**5 [2–18]**	NR	1 (2.5)	NR	ARDS 40 (100) ARF 6 (15) Cardiac failure 8 (20) Hepatic failure 4 (10)	29 (72. 5)	APACHE II >18 Dyspnoea Need for MV 1+ organ failure	NR

n: number of patients; (d): days. Incidence is reported as estimated rate of tuberculosis per 100,000 from gov.org last updated 2019 (high incidence is >40/100,000). All averages are mean ± SD unless stated otherwise; Median is signified in bold with (range) or [IQR]. APACHE II is worst score in 24 hours of admission. Mortality is reported as 'in-hospital mortality' unless stated otherwise. F: fatalities; S: survivors; NR: data not reported; MV: mechanical ventilation; DR%: percentage of patients with drug-resistant strains; ATT: anti-tuberculosis treatment; ARDS: acute respiratory distress syndrome; VAP: ventilator assisted pneumonia.

Table 7.3: Severity scoring for survivors vs fatalities

Study	Severity score	All patients	Survivors	Fatalities
Erbes et al.[14] (2006)	APACHE II	13±5.6	12.3±5.8	15.7±4.1
Lin et al.[43] (2009)	APACHE II	21±6.5	17.0± 5.8	23.2 ±5.8
Valade et al.[13] (2012)	SAPS II	31 (22–50)	28 (20–34)	50 (36–69)
Balkema et al.[29] (2014)	APACHE II	20.7±8.3	18.1±7.4	22.6±8.5
Lanoix et al.[31] (2014)	SAPS II	38 (6–121)	33.58±16.46	64.24±26.42
	SOFA	4 (0–17)	3 (0–15)	11 (0–17)
Rollas et al.[8] (2015)	APACHE II	21.5 (6–36)	17 (6–29)	27 (18–36)
	SOFA	6 (1–12)	4 (1–9)	9 (4–12)
Filiz et al.[57] (2016)	APACHE II	18 (7–32)	14 (7–21)	22 (16–32)
	SOFA	6 (1–14)	2.5 (1–7)	9 (2–14)
Duro et al. [46] (2017)	APACHE II	26 (15.75)	20.5 (17)	30 (12.75)
	SAPS II	55 (27.5)	42.5 (38.50)	58.0 (23.5)
Kim et al.[34] (2018)	APACHE II	19 (15–24)	18 (15–23)	21 (18–28)
	SOFA	8 (4–11)	7 (4–10)	9 (7–11)
Muthu et al.[42] (2018)	APACHE II	16.1±7.2	14.2 1±5.8	18.5 1±8.2
	SOFA	1.8±1.6	1 (1.4)	2.8 (3.3)
Tatar et al.[19] (2019)	APACHE II	22 (15–26)	17 (15–22)	23 (20–26)

Quality assessment of included studies

The Newcastle-Ottawa assessment scale (NOS) for cohort studies was used to assess study quality and risk of bias.[27] The Newcastle-Ottawa assessment scale evaluates three parameters; selection, comparability and outcome, awarding a certain number of points. The maximum number a study can receive is 9 points, indicating low risk of bias. Less than 5 points indicate a high risk of bias. The outcome used for the checklist was mortality.

Results

Characteristics of the studies

Seventeen out of 529 studies fulfilled the inclusion criteria and were included in the review. The studies ranged from 1995 to 2018. The studies included were from high (South Africa, South Korea, India) and low/intermediate TB incidence countries (Canada, Germany, Taiwan, France, Turkey, Portugal). All studies were retrospective except Balkema et al.[29] which was prospective. A total of 947 cases with active pulmonary TB who required ICU admission were included across all studies, of which 652 were male.

Quality of studies

Quality of studies was generally high when assessed using NOS checklist. Selection bias across studies was greatest risk due to clinician selected cohort groups, with small sample sizes. All had follow up resulting in outcomes with all subjects accounted for, and outcomes were clearly defined in all studies. No study had an overall outcome <7 points indicating low risk of bias (Table 7.4).

Table 7.4: Bias according to the Newcastle-Ottawa assessment scale[27]

Study	Selection score	Comparibility score	Outcome score	Total score
Penner et al.[32] (1995)	2	2	3	7
Erbes et al.[14] (2006)	2	2	3	8
Sharma et al.[20] (2006)	3	2	3	7
Ryu et al.[7] (2006)	2	2	3	7
Lin et al.[43] (2009)	2	2	3	7
Valade et al.[13] (2012)	2	2	3	7
Balkema et al.[29] (2014)	2	2	3	7
Lanoix et al.[31] (2014)	2	2	3	7
Rollas et al.[8] (2015)	2	2	3	7
Filiz et al.[57] (2016)	2	2	3	7
Kim et al.[21] (2016)	2	2	3	7
Pecego et al.[30] (2016)	2	2	3	7
Duro et al. [46] (2017)	2	2	3	7
Kim et al.[34] (2018)	2	2	3	7
Muthu et al.[42] (2018)	2	2	3	7
Tatar et al.[19] (2019)	2	2	3	7
Ferreira et al.[38] (2018)	2	2	3	7

To aid an inclusive qualitative analysis, the averages of medians and means were calculated, with each study weighted equally, regardless, of the number of cases. The mean or median age of cases ranged between 31.6–76.9 years with 12/17 studies having a mean/median age >41 years. Common comorbidities included HIV co-infection (27.1%), alcohol abuse (12.5%), diabetes (7.7%) and malnourishment (5.0%). 21% of cases were smokers. Thirty-eight % of cases had a diagnosis of TB prior to ICU admission. The most common indication for ICU admission was respiratory failure and ARDS (36.3%) followed by pneumonia (9.3%), sepsis (4.3%) and massive haemoptysis (3.8%).

Acute Physiology and Chronic Health Evaluation II was the most commonly used scoring system, reported in 13 studies, however SAPS II, quick Sequential Organ Failure Assessment (qSOFA) which identifies high-risk patients for in-hospital mortality with suspected infection outside the ICU and the Glasgow Coma Scale (GCS) were also used across the

studies. The average of the mean APACHE II score was 20.2 and median 19.1, across 8 and 6 studies respectively. The average of the median SAPS II score was 42.8 across 4 studies and median SOFA was 5.8 across 6 studies. The mean and median values for severity scores were consistently higher in fatalities than survivors in all studies except for Pecego et al. with survivors having a higher SAPS II score (Table 7.3).[30] The average of the mean APACHE II score was 22 and 16.4 for fatalities and survivors respectively across 5 studies. The average of the median of these scores were 23.3 and 16.5 for fatalities and survivors respectively, across 5 studies.

Individuals requiring mechanical ventilation ranged from 37.5% to 100%. Across all studies 67.2% of cases required mechanical ventilation and the duration in days was 14.5 and 13.25 days for the median and mean values respectively. There was a large variation for example Erbes et al. provide a mean of 26 and a range of 1–106,[14] similarly Lanoix et al.[31] provide a median of 8 with an interquartile range (IQR) of 1–129.

Duration of hospital stay was reported in 9 studies. The average of the median was 20.2 days across 6 studies and for the mean 51.2 days across 3 studies. The duration of ICU stay was reported in 14 studies, the average of the median was 7.8 days across 9 studies and mean was 15.6 across 4 studies. Similarly, for the duration of stay for both hospital and ICU, there was a large spread of data throughout some studies, reflected by the large interquartile ranges in Table 7.2.

Delay in initiation of anti TB treatment (ATT) within hospital was only reported in 8 studies, the lowest being 0 days and the largest mean value was 45 days in Penner et al.[32] The prevalence of drug resistance pattern was reported in 11 studies and ranged between 0% to 28.6%, 4.9% of cases having drug-resistant strains when combining all studies. Steroids were given to 11.5% of cases and vasopressor support was given to 15.0% of cases. Other treatment management was given to a smaller number of individuals including extracorporeal membrane oxygenation, tracheostomy and renal replacement therapy.

The most common reported complication was ARDS affecting 19.5% of all cases, followed by ventilator associated pneumonia (10.8%), multiple organ failure (10.5%), sepsis (9.5%) and hospital acquired infections (8.2%). Other reported complications included shock, disseminated intravascular coagulation, acute kidney infection, single organ failure and pneumothorax. In-hospital mortality ranged from 29% to 95.1% giving a mortality rate of 52.9% across all studies. In two studies a lower ratio of arterial oxygen tension to fractional inspired oxygen (PaO_2/FiO_2) indicated a poorer prognosis.[33,34] Causes of death were reported in 6 studies with septic shock and organ failure (including respiratory failure)

with respective values of 4.7% and 3.8% of total cases as the most common causes. Other causes of death included hospital acquired infection, raised intracranial pressure, pulmonary embolism and hypoxaemia.

No studies using first line intravenous anti TB medications in ICU were found.

Discussion

Acute respiratory failure, although a rare complication of TB, carries a high fatality rate. There is little research focus on the outcomes and factors affecting mortality in these patient groups, thereby hindering the ability of clinicians to change clinical practice and improve prognosis.

Mortality and ARDS

In this systematic review, average in-hospital mortality across 17 studies was 52.9%. This value is especially high considering availability and efficacy of ATT worldwide and the advancements in intensive care medicine. Attributable factors include delay in diagnosis and ATT initiation, altered drug absorption in critically ill patients, comorbidities and TB related complications. The most common complication and indication for ICU admission across the studies was found to be ARDS/acute hypoxaemic respiratory failure. Tuberculosis related acute respiratory failure carries a mortality rate of up to 60%, pneumonia carries a 25% mortality.[33,35,36]

Multiple organ failure and sepsis were present in 10.5% and 9.5% of cases respectively and were included as predictors of mortality in 9 studies. Three studies documented individuals with disseminated intravascular coagulation. This can be caused by miliary TB and is a negative predictor for survival, with individuals more likely to develop ARDS than those with isolated pulmonary TB; it carries a high mortality in the ICU setting, mostly attributed to septicaemia and subsequent multiple organ failure.[10] HIV/AIDS, alcohol abuse, diabetes, smoking status and chronic pancreatitis identified as independent risk factors for mortality.[14]

HIV and TB

Tuberculosis is the main cause of death in people living with HIV.[37] People living with HIV are 30 times more likely to develop active TB, with more severe and atypical pulmonary forms as the most common presentation.[38] Two studies reported an earlier age of hospitalisation and higher rate of respiratory failure.[30,38] Threshold for clinical suspicion should be lower in these individuals, given their diminished symptom presentation.[12,39]

ICU complications

Several ICU complications were reported. Critically unwell individuals are prone to drug interactions and adverse effects due to complex pharmacology, polypharmacy, disease severity and organ failure.[40] Hepatotoxicity is a particular risk with isoniazid, rifampicin and pyrazinamide. Patients with underlying hepatic sequelae including prior hepatitis, alcoholic liver disease are more vulnerable. Acute kidney injury and glomerular hyperfiltration can affect anti-TB drug elimination with pyrazinamide and ethambutol renally excreted.[41] Decompensated or end stage renal failure in ICU negatively influences patient outcome especially in those requiring dialysis, 45 individuals across these studies had renal failure.[14] Patients in multiple organ failure are less tolerant to the toxic side effects of anti-TB drugs, creating clinical dilemmas as therapy interruption can increase risk of drug resistance and death.

Hospital acquired infections (HAIs) were found to be a negative predictor of survival and were present in 8.2% of cases. Tuberculosis suppresses monocyte activity, causing immunosuppression and increasing infection risk.[42] Lin et al. reported nosocomial pneumonia incidence was four times higher in non-surviving individuals with pulmonary TB.[43] Ventilator associated pneumonia was found in numerous individuals who had been ventilated,[14] and was independently associated with hospital mortality.[14] Other infections include urinary tract and central venous catheter associated bloodstream infections which are associated with length hospital stay. Hospital acquired infections can prolong length of stay, contributing to an already elevated mortality rate.[44]

Diagnostic delay

Smear microscopy and culture have turnaround times of few days and several weeks respectively. GeneXpert NAAT TB-PCR test and urinary LAM (Fujifilm) may allow for results within hours.[9] Despite the growing availability of fast and reliable point of care tests, thinking of TB remains a challenge. Misinterpretation of clinical and radiological presentation, and lack of resources contribute to unreliable diagnosis and delays in treatment initiation. It can be challenging to radiologically distinguish TB from severe bacterial pneumonia as a cause of ARDS, many individuals are treated incorrectly before TB is considered in the differential. Empirical fluroquinolone could be beneficial covering both conditions, Tseng et al. reported oral fluoroquinolone usage as independently associated with better survival in those with TB mimicking severe pneumonia in ICU.[45]

Survival of individuals with TB can be significantly improved if therapy is started within 14 days of hospitalisation.[45] Erbes et al. found a significant increase in mortality in individuals not receiving optimal treatment including isoniazid and rifampicin.[14] In addition, Duro et al. found that starting ATT within 3 days of ICU admission improved survival.[46] Two studies with the longest delay in treatment initiation were from lower incidence countries.[13,32] Delays are common in areas with fewer TB cases, probably as a result of lack of experience.[47] Almost half of the studies did not report on treatment delay. The variation in delay ranged from 0–45 days globally, and may contribute to poorer prognosis. This review found only 38.3% of individuals diagnosed prior to admission.

Drug resistance

Rifampicin resistance is increasing and a major threat, with half a million people currently estimated to be infected with rifampicin resistant strains carrying a higher mortality.[2,24] The number of individuals with drug-resistant TB was 46 (4.9%). Drug resistance may have been under reported in these studies and this might explain why resistance was not found to be a predictor of mortality.

Intravenous anti-TB treatment

Tuberculosis treatment in ICU is complicated by organ dysfunction, drug toxicity and sub-therapeutic levels. First line drugs such as rifampicin and isoniazid are generally well absorbed when administered orally at the correct dose. In critically unwell individuals, absorption and pharmacokinetic drug properties are altered. The pharmacokinetic profile of anti-TB drugs has shown that there is a dose dependent relationship between concentration and clinical outcomes.[48] Critical illness alters gut motility, impairs mucosal barrier integrity, distorts commensal flora, delays gastric emptying leading to reduced absorption.[10,25,49] Hypoalbuminemia was found to be a predictor of mortality in this review with 47 individuals suffering from malnutrition pre-admission.[38] Hypoalbuminemia may lead to oedema, increasing the volume of distribution of drugs, as well as impair drug absorption all leading to lower drug concentrations in serum.[41,50] Parenteral administration or higher doses of drugs may be required to reach therapeutic effect.

Although no studies regarding intravenous antibiotics were found, a study by Ruslami et al. suggested a role for their use.[25] They compared patient groups over 2 weeks, administering standard oral versus a 33% higher dose of intravenous rifampicin, finding a three times higher ‘geometric mean area under the time concentration curve’ up to 6 hours, in the intravenous group. Mortality was substantially lower in individuals given intravenous

rifampicin with no reported increase in toxicity. They also found an increased survival compared to the standard oral dose, including more rapid resolution of coma and reduced mortality at 2 months and 8 months.[25] Koegelenberg et al. investigated the pharmacokinetics of enteral anti-TB drugs in intensive care individuals, finding that a fixed dose of rifampicin administered via nasogastric tube resulted in sub-therapeutic plasma concentrations in the majority of individuals.[48]

Although intravenous rifampicin is available, it is not widely accessible in low income countries.[51] Other first line drugs are not always accessible or available,[48] with no intravenous ATT formulation included current WHO Model List of Essential Medicines (2019).[52] This leads to use of second line drugs such as fluroquinolones and aminoglycosides in the ICU setting.[53]

Mechanical ventilation and steroids

Several studies identified mechanical ventilation as a risk factor for mortality.[8,31] The four highest mortality rates reported were from Kim et al. 2016 (95.1%),[21] Ferreira et al. (78.3%),[38] Tatar et al. (72.5%),[19] and Penner et al. (69.0%),[32] having the highest proportion of mechanically ventilated individuals (75–100%). Studies with the lowest proportion of mechanically ventilated individuals had the lowest reported mortality, such as Erbes et al.[14] with 37% ventilated and 25.9% mortality.[13,14,31] Those with more severe, disseminated forms of disease were more likely to require mechanical ventilation and develop ARDS, reflecting a referral bias, most unwell more likely to die.[12] Duration of mechanical ventilation has been associated with worse prognosis, possibly due to more HAIs, and pneumothorax.[14]

Adjuvant corticosteroid use is indicated for meningeal and pericardial disease, and pulmonary TB related ARDS.[12,46] Some studies have shown that systemic glucocorticoids are associated with improved prognosis, however this was non-specific for the critically unwell population.[54] The benefit of steroid use in TB individuals in ICU specifically remains unclear. We found that steroid use did not alter prognosis. Vasopressor support was found to be a predictor of fatality.

Severity scoring systems in ICU

Scoring systems for critically ill individuals are commonly used for estimating general ICU mortality, guiding clinical decision making and influencing distribution of hospital resources.[56] Individuals with a higher mortality risk may benefit from earlier, targeted and potentially more aggressive treatment, given the small intervention window and a higher risk of death; this may outweigh risk of iatrogenic harm.[55]

Many studies have shown APACHE II and SAPS consistently underestimate mortality among individuals with pulmonary TB, especially those with ARDS and the mechanically ventilated.[56,57] This highlights a shortfall in accurate risk stratification in these individuals, with a need for better tailored, ARDS specific scoring systems. APACHE does not include mechanical ventilation as an adverse outcome predictor a factor in its inaccuracy.[22] In the literature it has been reported than an APACHE score >18 is associated with a higher mortality giving a predicted mortality of >29%.[41] The average of mean APACHE II produced about 36% predicted mortality and using median a value about 32%. The median SAPS II and SOFA scores gave an estimated about 25% and <10% respectively. Most of these results drastically underestimate the calculated mortality of 52.9%. The data set in Table 7.3 showed that the fatalities vs survivors had a higher score throughout (except for Pecago et al.[30]).

Villar et al. designed an outcome score calculating 24hr post ARDS diagnosis, age, PaO_2/FiO_2 and plateau pressure.[55,58] Similarly Kim et al. developed a mortality prediction model for individuals with TB-destroyed lung on mechanical ventilation.[34] This model included age, vasopressor use, PaO_2/FiO_2 ratio and Brain Natriuretic Peptide (all predictors of ICU mortality in these individuals) finding this score more accurate at mortality prediction than APACHE II and SOFA.[34] Lung injury severity 24 hours after ARDS onset is a key determinant of outcome, reflecting the necessity for a reliable mortality prediction.[55] Two studies found a low PaO_2/FiO_2 ratio to be a predictor of fatality.[33,34] Although promising results have been obtained, further studies with perhaps additional variables are needed for external validation.[59]

High vs low burden areas

Nine out of the 17 studies were from high burden areas. Percentage of individuals diagnosed before admission was higher in low prevalence, resource rich areas, ranging from 53.8% to 75% over 4 studies (one not reported).[13,14,31,32] In comparison to 24.4% to 38.6% (two not reported) over 4 studies,[21,29,34,43] showing that more individuals are living with undiagnosed tuberculosis in poorer areas. This difference may be due to better diagnostic tools available in wealthier regions. The mortality in the low prevalence areas was 41.5% compared to the high prevalence at 64.9% with the highest mortality being the Kim et al. 2016 study at 95.1%.[21] The association between TB and low-income areas is known, with poverty being a cause and consequence of infection. Many risk factors for disease reactivation and predictors of mortality in ICU are associated with a lower socio-economic background, including HIV infection, malnutrition, alcohol use disorder and smoking.

More individuals were mechanically ventilated in high prevalence areas with higher mortality. Mechanical ventilation remains a predictor of mortality even in low burden areas. In these areas renal failure, sepsis, ARDS and APACHE II scoring are non-specific risk factors to TB.[31] There was no difference in the APACHE II score, in contrast to the differing mortality rates between the grouped studies. This may reflect the inefficiency of severity scoring systems to accurately estimate mortality in critically unwell TB individuals.

Limitations

This review only included individuals admitted to ICU which may reflect referral bias, as some lower income countries may not have had access to ICU beds. There was study heterogeneity in data reported, making meta-analysis challenging. No publication bias was assessed due to small sample sizes. No long term outcomes were reported.

Conclusion

The results across this review and previous literature are varied, reflecting the heterogeneity of patient presentation and aetiology of illness. The studies had relatively small sample sizes sand all save one were retrospective. There was disproportionate and variable mortality across studies only one-third of individuals were accurately diagnosed initially and 5% completed treatment successfully, highlighting the overwhelmingly poor outcomes for these individuals. A large number of individuals are undiagnosed until acutely unwell, leaving a small window for prompt diagnosis and treatment. Therapeutic intervention might be improved by administration of intravenous ATT, and may reduce complications and mortality. Current severity scoring systems underestimate mortality in ARDS related tuberculosis.

Though TB is treatable, individuals admitted to ICU with TB have an uncertain and desperate fate confronted with high mortality and plethora of complications, barriers to diagnosis and treatment challenges. Practice within ICU may need to change to detect and treat TB earlier and more aggressively, in order to improve outcomes. Tuberculosis in critically ill patients continues to be associated with significant mortality.[60]

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Chapter 8

Drug management of TB in the intensive care setting: an international multicentre study

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Summary

Background: Individuals requiring admission to an intensive care unit (ICU) due to TB have complex clinical presentations and high mortality rates. There is a clear knowledge gap on how to optimally manage treatment.

Objective: To evaluate the treatment outcomes of TB patients in ICU and explore the potential benefits of intravenous (IV) TB treatment regimens.

Methods: A retrospective observational multicentre study was conducted by the International Severe TB and Rehabilitation Working Group of the Global Tuberculosis Network (GTN). The study included TB patients aged >15 years admitted to ICUs in Europe, Asia and Latin America from January 1, 2005 to December 31, 2018. Data on demographics, microbiology, clinical information and treatment outcomes were collected and analysed.

Results: The study enrolled 434 cases. Over half were sputum smear-positive and 85.7% were culture-positive. Most required invasive mechanical ventilation, vasopressor support and steroids. Only 48.4% had TB medications initiated before or during ICU admission. The overall mortality rate was 54.8%, with 33.4% achieving treatment success. IV anti-TB drugs were administered to 43% of participants, with levofloxacin and amikacin being the most used. IV treatment longer than 10 days was associated with better outcomes. Individuals receiving IV rifampicin had a lower mortality rate (35.7%) compared to those who did not receive it (51.7%), p=0.05.

Conclusions: High mortality rates in ICU indicate the need for improved management strategies. The use of IV TB drugs, especially IV rifampicin, show potential benefit, suggesting the need for further prospective studies. Early screening and standardized treatment protocols could improve patient outcomes in high-incidence areas.

Introduction

Worldwide, TB is the leading infectious killer.[1–3] A recent systematic review on TB in the intensive care unit (ICU) setting reported that the majority of studies were retrospective small single centred studies and included a large heterogeneity of TB presentations such as respiratory failure, acute respiratory distress syndrome (ARDS), renal and multi organ failure among others,[4–6] and only a third of cases were started on TB treatment.[7] Several studies have demonstrated that mortality of TB on ICU is high (>50%).[8] Severe extrapulmonary forms such as miliary, disseminated and central nervous system (CNS) or TB meningitis, frequently require hospitalisation and admission to ICU. Despite being critically ill, individuals often receive treatment with oral TB drugs including administration via a nasogastric tube when mechanically ventilated.[4–6,8–14] Critical illness can affect TB drug pharmacokinetics as individuals may suffer from altered absorption, clearance, having a larger distribution volume, hypoalbuminemia and liver and/or renal impairment.[15] Furthermore, absorption of isoniazid and rifampicin and subsequent bioavailability can be significantly reduced when crushed and administered together with enteral nutrition via a nasogastric tube due to food effect.[6,7,11,16] Intravenous (IV) drug administration could be an option as an adjunct to, or in the place of, oral anti-TB therapy in ICU settings as it may ensure that target levels are reached rapidly at the site of infection to accelerate a reduction in bacillary loads,[17–19] and reduce mortality. However, evidence and guidance on such treatment are not currently available in TB management guidelines.[3]

The aim of our study is to determine treatment and outcome of TB patients admitted to ICU and explore whether the use of IV TB treatment regimens could improve patient survival.

Methods

The 'International Severe TB and Rehabilitation Working Group' of the Global Tuberculosis Network (GTN), conducted this large observational cohort study using the same methodology as in previous GTN studies.[20,21]

Participants

A retrospective observational multi-centre study was conducted including all consecutive individuals with pulmonary and extrapulmonary TB aged >15 years, admitted to ICU in Europe, Asia and Latin America from January 1st 2005 to 31st December 2018, this included patients going to ICU due to single or multiorgan failure due to TB or patients with TB admitted due to

other reasons. Data on demographic, microbiological, and clinical information were collected from the medical records (online Supplementary Data). WHO TB Outcomes were stratified by route of TB drug administration.[22] Treatment success was defined as the sum of cured and treatment completed, without bacteriological evidence of failure.[22]

Statistical analysis

A descriptive analysis was performed on the cohort. Qualitative variables were described as absolute and relative (percentage) frequencies, whereas quantitative variables were summarized with mean (standard deviations, SD) or median (interquartile ranges, IQR) in case of parametric and non-parametric distribution, respectively. Between group comparisons of qualitative variables were assessed with the Chi-squared or Fisher exact tests whereas the comparison of quantitative variables were performed with the Student-t and the Mann-Whitney tests for parametric and non-parametric variables, respectively. Logistic regression analysis was conducted to assess the relationship between epidemiological, clinical variables and outcomes. The 10-day duration of IV treatment was selected following that it was the median value measured. A two-tailed p-value less than 0.05 was considered statistically significant. STATA version 17 (StataCorp, TX) was used to perform statistical computations.

Ethical statement

The study was registered and approved as a Quality Improvement Project no. 8485, 16/08/2017 at the Barts Health NHS Trust, London, UK. Given the retrospective design the need for written informed consent was waived. The participating centres received ethics approval as per local ethics guidelines.

Results

Baseline characteristics on admission to the ICU

We enrolled 434 cases into the study. Distribution of participants among centres varied (Table 8.1). Almost 60% of cases were collected from several centres in two cities (London and Porto Alegre), whereas four centres collected fewer than 10 cases. Over half of participants were sputum smear-positive, and 85.7% of participants were sputum culture positive. The majority of participants were males, almost 60% had undergone BCG vaccination and about a third of cases were living with HIV. All participants had been admitted after a median symptomatic time of 21 days (IQR 7–45). Mean (SD) SAPS II and SOFA score on

admission to the ICU was 47.5 (18.1), and 9.8 (4.5) respectively. The main reasons for admission to ICU were acute respiratory failure (ARF), multi organ failure, TB meningitis, massive haemoptysis, and airway obstruction (Table 8.2).

Table 8.1. Participants included by centre and country (total n=434)

Country	Centre/hospital	Number of patients
The Netherlands	Groningen	3
Portugal	Porto	5
Sweden	Stockholm	8
United Kingdom	London	101
China	Hong Kong	43
Mexico	Mexico City	20
	Monterrey	45
Brazil	Manaus	12
	Rio de Janeiro	17
	Porto Alegre	157
Paraguay	Asuncion	16
Peru	Lima	7

Table 8.2. Baseline demographics and risk factors of TB patients admitted to intensive care (n=434)

Variables	
Median (IQR) age at the admission, years	45 (33–59)
Age at admission (WHO age groups), n (%)	
15–24 years	37 (8.6)
25–34 years	87 (20.1)
35–44 years	84 (19.4)
45–55 years	80 (18.5)
55–64 years	66 (15.2)
≥65 years	79 (18.2)
Males, n (%)	290 (66.8)
Smoking history, n (%)	154 (35.4)
Alcohol abuse, n (%)	102 (23.5)
Type 2 Diabetes, n (%)	68 (15.7)
Immunosuppression, n (%)	128 (29.5)
BCG vaccinated, n (%)	260 (59.9)
HIV positive, n (%)	138 (31.8)
Median (IQR) CD4 count this latest TB episode	52 (24–108)
AIDS, n (%)	129 (29.7)
Drug abuse, n (%)	58 (13.4)
Employment, n (%)	221 (50.9)
Migrant status, n (%)	95 (21.8)
Prior anti-TB therapy, n (%)	66 (15.2)
Surgery for TB, n (%)	17 (3.9)

Management and treatment

The vast majority of participants (82.5%) required invasive mechanical ventilation with a median (IQR) duration of 7 (3–14) days. Two thirds of participants received vasopressor support and almost 70% steroids. Fewer than half of participants had TB medications initiated during the ICU admission (48.4%) see Table 8.3.

Table 8.3. Management of TB patients admitted to intensive care (n=434)

Variables	
Hemofiltration n (%)	43 (9.9)
Dialysis, n (%)	83 (19.1)
Vasopressor exposure, n (%)	298 (68.6)
Corticosteroids exposure, n (%)	294 (67.7)
Start of TB medications during ICU admission, n (%)	212 (48.4)
Treatment duration after TB diagnosis, months, Median (IQR)	6 (3–7)
IV TB drugs given, n (%)	180 (41.4)
IV treatment for TB, days, Median (IQR)	10 (4–20)
IV rifampicin, n (%)	42 (9.67)
Non rifampicin IV TB first line or repurposed, n (%)	79 (18.2)
IV TB drug for CNS TB, n (%)	20 (11.1)
IV TB drug for malabsorption, n (%)	86 (47.7)
IV TB drug for MDR/XDR-TB, n (%)	14 (7.8)
IV TB drug for liver sparing regimen, n (%)	46 (25.5)
Glasgow Coma Scale, Median (IQR)	15 (8-15)
Sputum Smear positive, n (%)	222 (51.1)
Culture positivity, n (%)	372 (85.7)
GeneXpert positivity, n (%)	73 (16.8)
Resistance to isoniazid, n (%)	22 (5.1)
Resistance to rifampicin, n (%)	23 (5.3)
Charlson Comorbidity Score, Median (IQR)	3 (1–6)
SAPS II, Mean (SD)	47.5 (18.1)
Sofa score, Mean (SD)	9.8 (4.5)
Intubated, n (%)	358 (82.4)
Mechanical ventilation on admission, n (%)	296 (68.2)
Duration of mechanical ventilation, days, Median (IQR)	7 (3–14)

Clinical outcomes

More than half of admitted individuals died (54.8%) and 145 (33.4%) achieved treatment success, 2.5% were lost to follow up and the remainder on treatment (Table 8.4).

Table 8.4. Treatment outcomes for TB patients admitted to intensive care (n=434)

Variables	
Sputum smear conversion, days, Mean (SD)	52.3 (27.3)
Culture conversion, days, Median (IQR)	45 (30–84)
Final treatment outcome, n (%)	
Cured	93 (21.4)
Treatment completed	52 (12)
Still on treatment	11 (2.5)
Died	238 (54.8)
Lost to follow-up	11 (2.5)
Treatment failed	0 (0.0)
Not evaluated	16 (3.7)
Treatment success	145 (33.4)

Determinants of clinical outcome

Several variables were associated with unfavourable treatment outcomes including higher age, immune suppression, markers of severe TB disease and comorbidity (Table 8.5). In total, 212 (48.8%) patients commenced anti-TB treatment before or during ICU admission: which was associated with a favourable outcome OR 1.99 (1.30–3.06) (p=0.002) in the univariate analysis but was not significant in the multivariate analysis 1.71 (0.63–4.67) (p=0.29). Positive sputum smear and culture parameters were not associated with treatment outcome. Starting TB treatment on the ICU and being a migrant were predictors of favourable in univariate analysis but in the multivariate there was only a trend of more severe outcome with increasing age (Table 8.5). As expected, markers of disease severity and co-morbidity were interrelated, and some were not independently related in the multivariate analysis.

When considering 30-day mortality as the outcome measure, the factors associated with higher mortality were HIV, immunosuppression (non-HIV), need of intubation, dialysis, vasopressor exposure and corticosteroid exposure in the univariate but not the multivariate analysis (Table 8.6). A trend towards increasing mortality was noted in the elderly 55–64 years OR 8.28 (0.97–70.85) p=0.05 and >65 years OR 9.46 (0.88–101.88) p=0.06 in the multivariate analysis. Each additional point in Charlson Comorbidity index, the Sequential Organ Failure Assessment score, and the Simplified Acute Physiology Score >49; increased mortality 1.72-fold (p<0.005), 1.6-fold (p<0.0001) and 8.5-fold p<0.0001 respectively. The Glasgow coma scale demonstrated a 10% lower risk of death for every unit increase on the scale.

Table 8.5. Logistic regression analysis to assess the relationship between clinical variables and treatment success (Model 1: treatment success vs death)

	Univariate analysis		Multivariate analysis	
Variables	OR (95% CI)	p-value	OR (95% CI)	p-value
Age at admission (WHO age groups)				
15–24 years	REF.	REF.	REF.	REF.
25–34 years	1.12 (0.47–2.62)	0.79	0.48 (0.09–2.44)	0.38
35–44 years	0.88 (0.37–2.09)	0.78	0.47 (0.09–2.59)	0.39
45–55 years	1.01 (0.42–2.39)	0.99	0.59 (0.10–3.48)	0.56
55–64 years	0.56 (0.22–1.39)	0.21	0.15 (0.02–1.37)	0.09
≥65 years	0.44 (0.18–1.06)	0.07	0.13 (0.02–1.07)	0.06
Males	1.04 (0.67–1.60)	0.87	1.73 (0.63–4.80	0.29
Diabetes	0.57 (0.31–1.06)	0.08		
Immunosuppression (non-HIV)	0.33 (0.19–0.55)	<0.0001	0.57 (0.19–1.67)	0.30
HIV status	0.91 (0.58–1.42)	0.68		
Migrant status	2.06 (1.25–3.39)	0.004	1.45 (0.37–5.72)	0.59
ICU admission for multi organ failure	0.51 (0.30–0.87)	0.01	0.30 (0.06–1.40)	0.13
Mechanical ventilation	0.21 (0.11–0.39)	<0.0001	0.88 (0.16–4.98)	0.88
Dialysis	0.46 (0.26–0.82)	0.008	0.54 (0.18–1.68)	0.29
Vasopressor use	0.22 (0.14–0.36)	<0.0001	0.42 (0.11–1.60)	0.20
Corticosteroids exposure	0.54 (0.34–0.84)	0.007	0.46 (0.12–1.82)	0.27
Start of TB medications during ICU admission	1.99 (1.30–3.06)	0.002	1.71 (0.63–4.67)	0.29
Treatment duration after TB diagnosis, months	1.24 (1.15–1.33)	<0.0001	1.24 (1.09–1.41)	0.0001
IV TB drugs given	0.77 (0.50–1.18)	0.22		
IV treatment for TB >10 days	2.48 (1.22–5.03)	0.01	1.96 (0.74–5.22)	0.18
Glasgow Coma Scale	1.17 (1.10–1.24)	<0.0001	1.12 (0.98–1.27)	0.09
Sputum Smear positive	0.92 (0.60–1.39)	0.68		
Sputum Smear conversion, weeks	0.99 (0.97–1.03)	0.73		
Culture positivity	1.64 (0.74–3.67)	0.22		
Charlson Comorbidity Score ≥3	0.58 (0.38–0.87)	0.01	1.32 (0.44–4.02)	0.62
SAPS II ≥49	0.12 (0.04–0.33)	<0.0001		
Sofa score	0.70 (0.58–0.86)	<0.0001		

Intravenous TB treatment regimen and clinical outcomes

At least one anti-TB drug was administered intravenously to 180 (43%) participants; levofloxacin (n=95) and amikacin (n=85) were the most commonly administered IV agents, whereas only 9.7% received IV rifampicin. The mean number of IV agents used was two (1–6). Intravenous anti TB drugs were prescribed because of suspected malabsorption in 47.7%, TB meningitis in 11.1%, or as a liver sparing regimen in 25.5% of individuals with drug induced liver injury. There was a greater proportion of IV anti-TB drugs (first and second line) used in Europe than in Latin America or Southeast Asia: 56/117(47.8%), 99/274 (36.1%), and 16 (37.2%) participants respectively (p=0.01), due to availability. No first-line IV anti-TB drugs were available in Latin America. Median days of IV treatment

were ten (IQR 4–20). Treatment success did not differ significantly between oral and IV therapy; however, individuals undergoing IV treatment >10 days experienced a 2.5-fold better outcome (p=0.01) as compared to those with a shorter duration of IV drugs. Time to sputum smear and culture conversion did not differ between oral and IV therapy though sputum conversion occurred after a median of 43.4 (IQR) days in patients on IV treatment as compared to a median of 62.7 (IQR) days with oral treatment (p=0.22). Every additional day of IV drugs increased the odds of treatment success. When considering 30-day mortality, there was no increased risk of unfavourable treatment outcomes when IV treatment was given. Our data suggests that patients who received IV rifampicin had a lower mortality rate (35.7%) compared to those who did not receive it (51.7%), p=0.05.

Table 8.6. Logistic regression analysis to assess the relationship between clinical variables and 30-day mortality

	Univariate analysis		Multivariate analysis	
Variables	OR (95% CI)	p-value	OR (95% CI)	p-value
Age at admission				
15–24 years	REF.	REF.	REF.	REF.
25–34 years	1.21 (0.54–2.71)	0.64	3.75 (0.68–20.55)	0.13
35–44 years	1.30 (0.58–2.90)	0.53	4.27 (0.73–24.93)	0.11
45–55 years	1.13 (0.50–2.56)	0.77	5.04 (0.73–34.9)	0.10
55–64 years	1.61 (0.70–3.72)	0.26	8.28 (0.97–70.85)	0.05
≥65 years	2.17 (0.95–4.92)	0.07	9.46 (0.88–101.88)	0.06
Males	0.79 (0.53–1.19)	0.26	0.37 (0.13–1.05)	0.06
Diabetes	0.94 (0.55–1.59)	0.81		
Immunosuppression (non-HIV)	2.57 (1.66–3.97)	<0.0001	1.60 (0.59–4.31)	0.36
HIV status	1.53 (1.01–2.32)	0.04	0.38 (0.07–2.10)	0.26
Migrant status	0.23 (0.14–0.39)	<0.0001	0.29 (0.08–1.06)	0.06
Pulmonary form	1.42 (0.97–2.09)	0.08		
ICU admission for multi organ failure	1.53 (0.97–2.43)	0.07		
Mechanical ventilation	6.22 (3.15–12.28)	<0.0001	2.43 (0.45–13.1)	0.30
Dialysis	2.72 (1.62–4.57)	<0.0001	2.34 (0.78–6.99)	0.13
Vasopressor exposure	4.31 (2.68–6.94)	<0.0001	2.21 (0.61–7.92)	0.23
Corticosteroids exposure	2.30 (1.49–3.56)	<0.0001	0.97 (0.30–3.16)	0.95
Start of TB medications during ICU admission	0.57 (0.38–0.84)	0.004	0.62 (0.24–1.61)	0.33
Treatment duration after TB diagnosis, months	0.85 (0.80–0.90)	<0.0001	0.85 (0.75–0.95)	0.006
IV TB drugs given	0.95 (0.64–1.41)	0.80		
IV treatment for TB >10 days	0.43 (0.23–0.82)	0.01	0.54 (0.21–1.36)	0.19
Glasgow Coma Scale	0.89 (0.85–0.93)	<0.0001	0.93 (0.83–1.04)	0.19
Charlson Comorbidity Score ≥3	1.74 (1.18–2.56)	0.005	1.05 (0.20–5.42)	0.96
SAPS II ≥49	8.52 (3.50–20.77)	<0.0001		
Sofa score	1.66 (1.35–2.05)	<0.0001		

Discussion

To the best of our knowledge, this is the first study looking at the use of IV drugs for TB in ICU. We found that higher composite comorbidity and predictive scores were associated with a mortality rate of 56.5%, higher than that reported in other studies.[16,23–27] However there was significant heterogeneity: Hong Kong had fewer deaths (34.8%), as compared to Europe (41.17%) and Latin America (62.9%). More than half of participants treated in Hong Kong were cured (55.8%) compared to 34.4% in Europe and 11.1% in Latin America. This may in part be explained by the proportion of people living with HIV and immunocompromise, time to presentation and differing resources at the different sites and the availability of IV rifampicin.[28,29]

Our study evaluated the use of IV regimens in the ICU; median duration was ten days before switching to a full oral regimen; a duration longer than 10 days of consecutive IV anti-TB drugs, was associated with better survival. Treatment outcomes appeared better in our cohort with greater use of IV rifampicin (n=42; 10.1%) with 27 out of 42 (64.2%) individuals on IV rifampicin alive at day 30, although this was not statistically significant. Our study further highlights the lack of access to IV formulations of first-line anti-TB drugs in the Latin American countries participating in this study. Some countries may be able to obtain IV rifampicin; however, other first-line drugs are not always available in IV formulation.[30] Parenteral administration of medications allows them to reach target concentration/exposure, which may improve treatment outcomes and reduce mortality, especially in extensive high bacillary load infections when rapidly achieving higher drug exposures is vital. More importantly, the timing of parenteral administration of anti-TB drugs is critical and should be given as soon as possible. Levofloxacin and amikacin were the most used IV drugs in our cohort, likely used by the centres to enhance the bactericidal effect of TB treatment and as broad spectrum to cover additional bacterial infection, which are common in the ICU. Amikacin and streptomycin are bactericidal and associated with favourable outcomes.[31] In this study aminoglycosides were administered on average for only one day as part of local sepsis protocols.

We were unable to determine whether the dose and treatment intensification (more than 4 anti-TB drugs) had an impact on outcomes. Moreover, dose and treatment intensification could lead to more adverse events, which were not captured in this present study. A study looking at the addition of higher dose rifampicin plus levofloxacin in TB meningitis showed improved outcomes in isoniazid-resistant cases with early dose intensification.[32,33] A recent study has shown that the addition of levofloxacin (20 mg/kg) and rifampicin (15

mg/kg) may make a difference in survival in isoniazid-resistant cases.[32] A study conducted in Indonesia on TB meningitis patients receiving 33% higher dose of IV rifampicin (13 mg/kg) reported better outcomes when compared to standard oral therapy.[34] A phase 2 TB meningitis study in South Africa suggested that higher (35 mg/kg) oral doses of rifampicin achieved higher PK levels than IV rifampicin (20 mg/kg).[35] The parent study, LASER-TBM trial showed that high dose rifampicin and linezolid reduced mortality in people living with HIV with TB meningitis.[36] A recent metanalysis of high dose rifampicin did not reduce mortality in patients with TB meningitis; however, it did reach levels of plasma C_{max} and $AUC_{0\text{-}24h}$ consistent with IV therapy.[37] Ongoing trials in TB meningitis such as the HARVEST and INTENSE-TBM studies might confirm the potential benefit of high dose rifampicin (up to 35 mg/kg).[38,39]

Carbapenems and linezolid have also been used in case reports and may be achieve higher CSF (cerebro spinal fluid) concentrations than highly protein bound antimicrobials like rifampicin. However, TB meningitis comprised less than 10% of our cohort and it may not be possible to fully extrapolate this finding to pulmonary and other extrapulmonary presentations of TB. Although there is a rationale to extend duration of treatment in patients with extensive disease to prevent relapse,[40] it can be argued that intensified treatment including IV anti-TB therapy should be given tempestively in an ICU setting where mortality is high, and patients may not survive to complete a longer course of treatment. In the absence of IV rifampicin, IV antimicrobials, such as a later generation fluoroquinolone, amikacin and carbapenem, can be readily given in hospital in most countries and monitored: it is important to note that as *Mycobacterium tuberculosis* has β-lactamases, carbapenems would need to be given together with β-lactamase inhibitors. These may have the additional benefit of covering drug-resistant strains whilst awaiting DSTs. The COMRADE Trial demonstrated bactericidal activity of meropenem plus clavulanate was not affected by the presence of rifampicin in an early bactericidal activity study.[41] Further studies to determine the utility of dose intensification and IV administration of anti-TB drugs in especially severe extrapulmonary forms of TB (such as abdominal TB, TB spondylitis, miliary TB) are needed beyond TB meningitis to understand if an initial short 2- to 4-week course of IV anti-TB regimen can not only improve survival but also reduce TB complications and sequelae.[42] A randomized controlled trial in Ukraine evaluating the efficacy and safety of IV anti-TB medications in pulmonary TB was terminated by the sponsor in 2019 (NCT04150367) and the reason for termination and any results are unavailable.[43] Therapeutic drug monitoring, even though recently recommended for some patients including those in ICU, is not widely available and featured in only a handful of sites participating in our study: only 2% of our cohort

had rifampicin levels taken, of which a third had sub-therapeutic levels (sampling has the potential to tailor dosing to maximise efficacy, reduce toxicity and adverse events).[44,45] Novel point of care tests using saliva could be a cheaper and more suitable option when short turn-around times are required.[46–49]

Although this is a retrospective cohort study, there are several strengths. This is the largest study evaluating TB outcomes of people admitted to an ICU from low and high TB settings and the first to evaluate the use of IV antibiotics for TB. The dataset is rich in detail on management and treatment, which is uncommon for TB as it is mainly an outpatient-managed illness with challenges like non-adherence.[50,51] Furthermore, it highlights the large variability in how these cases are treated. However, our study also has several limitations. The time elapsed from data collection was long and complicated by lack of resource and later by the COVID-19 pandemic, which heavily affected our TB services.[52] Case-management was for the most part based on differing protocols/local guidelines/hospital policies and levels of resource; different study-populations; heterogeneity in number of individuals recruited; the retrospective design, varying availability of IV drugs during the long study period, variable duration, and dosage of IV treatment. All these factors could have affected our findings. As the study was retrospective, in some cases it was difficult to determine whether TB triggered admission to ICU or whether this was due to another cause (e.g., an additional bacterial infection). Moreover, we only evaluated critically ill patients admitted to ICU, therefore outcomes could be associated with other unmeasured variables. We did not assess issues related to mechanical ventilation and cannot exclude any influence due to ventilatory management. Intravenous administration, dose and treatment intensification could lead to more adverse events, which were not captured in this study. Despite these limitations, our study represents programmatic conditions, at a time when even randomized controlled trials are being questioned.[53] Last but not least, we had an incomplete dataset, and this further challenged the analysis – particularly the multivariate analysis – creating a large discrepancy in our results not confirmed in the multivariate as statistically significant covariates. The high percentage of missing covariate data, and the different approaches to handling missing covariate information, makes it difficult to interpret these results. The univariate analysis, while useful for initial observations, does not account for potential confounding factors and therefore should be interpreted with caution. The multivariate analysis, even though not statistically significant, is a more reliable indicator as it considers the influence of multiple variables simultaneously. We have used the latter unless otherwise stated.

Future perspectives to the management of TB in ICU could include adding TB to the initial assessments and screening for TB in high incidence settings, utilizing novel rule in or rule

out tests in development.[54] This could lead to commencement of anti-TB medications sooner, which may be of benefit to treatment outcomes. We demonstrate that predictive scores have the possibility to stratify prognostic risk and may help clinicians define individuals requiring admission to ICU and receive IV anti-TB drugs. Treatment intensification in this setting with higher dose oral rifampicin, and/or IV administration of first- and/or second-line TB drugs could make a step change difference in outcome. IV regimens or higher oral doses may be useful in ICU, and used as a bridging regimen to transition to a standard dose (as soon as the patient can absorb). Screening for TB and putting TB in the differential at entry into ICU in high incidence settings may improve outcomes by capturing some of the 50% of cases that go undiagnosed. Novel monitoring tools, like the Mycobacterial Load assay, transcriptomics, R/S ratio might in future be able to better determine response to treatment without the delay of traditional culture-based methods. Also, therapeutic drug monitoring could be a useful tool in achieving therapeutic levels of antimycobacterial drugs.[55–57] Altogether, in the near future these tools could better optimize the management of TB in the ICU setting. Prospective studies in this setting are required to further evaluate whether quicker implementation of treatment including IV TB drugs, standards and guidelines can reduce variability in care and improve outcomes.

Our study emphasizes the critical challenges and high mortality associated with TB in the ICU setting. Despite the significant heterogeneity in patient presentations and treatment protocols across different regions, our findings highlight several key insights that could inform future TB management strategies in ICUs. First, the high mortality rate of 56.5% in our cohort, highlights the need for improved diagnostic and treatment approaches. The variability in outcomes among different regions suggest that resource availability, timely diagnosis, and access to IV formulations of TB drugs may play crucial roles in patient survival. Second, our data indicate that the use of IV TB drugs, particularly IV rifampicin, may be associated with better survival outcomes, although this finding was not statistically significant. Patients receiving IV rifampicin had a lower mortality rate compared to those who did not receive it, suggesting a potential benefit that warrants further investigation. Our study portrays the potential advantages of IV drug administration in ensuring rapid achievement of therapeutic drug levels, which is particularly important in critically ill patients with altered pharmacokinetics. The observed trend towards better outcomes with longer durations of IV treatment (>10 days) further supports the need for prospective studies to evaluate the optimal duration and combination of IV TB regimens. Our study reveals significant variability and gaps in current TB management guidelines. The lack of standardized protocols and the variability in drug availability and usage stresses the need for robust

clinical trials to establish evidence-based guidelines for the use of IV TB medications in ICU settings. Future research should focus on the early identification and treatment of TB in ICU patients, potentially through routine screening in high-incidence areas. Prospective studies should also evaluate the use of novel diagnostic tools to expedite treatment decisions, the impact of higher dose oral and IV TB drugs on treatment outcomes, and the role of therapeutic drug monitoring.

Conclusion

Our study provides valuable insights into the management and outcomes of TB in ICU settings. Whilst there was an indication that IV rifampicin is linked to reduced mortality, this association was not statistically significant. There is a critical need for more rigorous research to develop standardized treatment protocols. By addressing these gaps, we can improve the prognosis for critically ill TB patients and reduce the high mortality associated with this condition.

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Chapter 9

Nederlandse samenvatting

Dit proefschrift onderzoekt de behandeling van patiënten met multidrugresistente (MDR) en extensief drug resistente (XDR) tuberculose (TB), zowel binnen als buiten de intensive care unit (ICU). Het werk is verdeeld in twee hoofdonderdelen: het gebruik van bèta-lactam antibiotica en de behandeling van TB in de ICU. Beide delen bieden waardevolle inzichten in de therapeutische mogelijkheden en uitdagingen bij de behandeling van resistente TB.

Deel 1: Bèta-lactam antibiotica

Het eerste deel van het proefschrift richt zich op het gebruik van carbapenems (zoals meropenem en imipenem) in combinatie met bèta-lactamase remmers zoals clavulaanzuur. In **hoofdstuk 2** wordt een multicentrische observationele studie gepresenteerd waarin meropenem/clavulaanzuur vergeleken wordt met imipenem/clavulaanzuur bij MDR- en XDR-TB. Meropenem/clavulaanzuur bleek effectiever, met hogere sputum- en cultuurconversiepercentages en betere behandelresultaten. Beide behandelingen werden goed verdragen.

Hoofdstuk 3 bevestigt de effectiviteit van meropenem/clavulaanzuur, zelfs bij patiënten met ernstige ziekte en veel resistentie tegen de middelen tegen TB. Ondanks de ernst van de ziekte was het percentage van sputumkweek conversie vergelijkbaar met die van de controlegroep. Bijwerkingen waren voornamelijk mild en gastro-intestinaal van aard.

In **hoofdstuk 4** wordt imipenem/clavulaanzuur toegevoegd aan een geoptimaliseerd achtergrondregime (OBR) van minimaal 20 maanden. De resultaten tonen aan dat deze toevoeging geen significante verbetering in behandeluitkomsten oplevert ten opzichte van OBR alleen.

Hoofdstuk 5 beschrijft een casus van een patiënt met XDR-TB die het Fanconi-syndroom ontwikkelde tijdens langdurige behandeling met meropenem/amoxicilline-clavulaanzuur. Dit benadrukt het belang van niermonitoring bij langdurig gebruik van deze combinatie.

Dit proefschrift bespreekt ook de farmacodynamiek van bèta-lactams, waarbij het tijdsinterval boven de minimale inhiberende concentratie (T>MIC) cruciaal is voor effectiviteit. Meropenem, een tijdsafhankelijke antimicrobiële stof, toont betere resultaten bij driemaal daagse toediening dan bij eenmaal daagse toediening.

Nieuwe orale carbapenems zoals tebipenem en sanfetrinem bieden perspectief voor bredere toepassing, vooral in landen met beperkte middelen. Sanfetrinem toont sterke activiteit tegen MDR- en XDR-TB en is momenteel in klinische ontwikkeling. Daarnaast worden cephalosporines zoals cefadroxil en cephalexin genoemd als potentieel effectieve orale opties.

Een belangrijk aandachtspunt is het risico op antimicrobiële resistentie door ongereguleerd gebruik van orale penems zoals faropenem, vooral in Azië. Faropenem heeft intrinsieke activiteit tegen Mtb, maar klinische studies tonen beperkte effectiviteit. Dit proefschrift pleit voor wereldwijde regulering van het gebruik van deze middelen om resistentie te voorkomen.

Deel 2: Tuberculose in de intensive care unit

Het tweede deel van dit proefschrift richt zich op de behandeling van TB in de ICU. **Hoofdstuk 6** bevat een systematische review van 17 studies met in totaal 947 patiënten. De sterfte varieerde van 29% tot 95%, met een gemiddelde van 52,9%. De meest voorkomende reden voor ICU-opname was acute respiratoire insufficiëntie. Slechte prognostische factoren waren ziekenhuisinfecties, mechanische ventilatie, vertraagde behandeling, orgaanfalen en hoge ernstscores. Bestaande scoringssystemen zoals APACHE II onderschatten vaak de sterfte bij TB-patiënten.

Hoofdstuk 7 presenteert een internationale multicentrische studie van 434 TB-patiënten in ICU's in Europa, Azië en Latijns-Amerika. Slechts 48,4% kreeg TB-medicatie vóór of tijdens ICU-opname. De sterfte was 54,8%, en slechts 33,4% bereikte behandelsucces. Intraveneuze (IV) behandeling werd toegepast bij 43% van de patiënten, met levofloxacine en amikacine als meest gebruikte middelen. IV toediening van rifampicine was geassocieerd met een lagere sterfte (35,7% versus 51,7%).

De studie benadrukt de noodzaak van verbeterde behandelstrategieën, waaronder vroege screening en standaardisatie van behandelprotocollen. IV behandeling, vooral met rifampicine, lijkt voordelen te bieden, maar toegang tot deze middelen varieert sterk per regio.

Algemene discussie en toekomstperspectieven

Dit proefschrift onderstreept het potentieel van bèta-lactams in de behandeling van resistente TB, vooral in combinatie met clavulaanzuur. Nieuwe orale formuleringen kunnen de toegankelijkheid to deze middelen vergroten en ziekenhuisopnames verminderen. Tegelijkertijd is er bezorgdheid over resistentieontwikkeling en verstoring van het microbioom door breed-spectrum antibiotica.

Voor ICU-patiënten biedt IV behandeling voordelen in termen van snellere en adequate medicijnspiegels en betere uitkomsten, maar brengt ook risico's met zich mee zoals

lijninfecties en leverfunctiestoornissen. De ontwikkeling van orale alternatieven zoals sanfetrinem en tebipenem kan deze uitdagingen helpen overwinnen.

Dit proefschrift pleit voor:

- Prospectieve studies om de effectiviteit van IV en orale bèta-lactam antibiotica te bevestigen.
- Verdere ontwikkeling van orale carbapenems en cephalosporines.
- PK/PD-onderzoek om optimale dosering en weefselverdeling te bepalen.
- Monitoring van resistentieontwikkeling.
- Standaardisatie van behandelprotocollen, vooral in gebieden met minder middelen.
- Vroege screening en tijdige start van behandeling van TB in ICU's.

Chapter 10

Summary and general discussion

In this thesis we address key topics encountered by people with drug-resistant (DR) tuberculosis (TB) in and outside the intensive care unit (ICU). The first part of the discussion focuses on treating patients with multidrug-resistant (MDR)-TB with repurposed drugs like carbapenems with beta-lactamase inhibitors. The second part of the discussion reports on the management of TB in the ICU and evaluates the use of intravenous drugs versus oral drugs.

Notably, this thesis provides insights on the current gaps in management of TB patients with extensively drug resistance (XDR) and severe forms of the disease.

Summary

PART 1, beta-lactams

In **chapter 2** we present a multicenter observational study comparing the effectiveness and safety of imipenem/clavulanate versus meropenem/clavulanate in treating MDR and extensively drug-resistant XDR TB. The study included 180 patients, of which 96 were treated with meropenem/clavulanate and 84 with imipenem/clavulanate. Our results showed that meropenem/clavulanate was possibly more effective, with higher sputum smear and culture conversion rates and better treatment success rates compared to the imipenem/clavulanate group. Adverse events were rare and similar between the two groups, indicating that both regimens were well tolerated.

The findings from this chapter are significant for people with MDR- and especially people with bedaquiline resistant XDR-TB with few therapeutic options. Furthermore the study highlights that meropenem/clavulanate-containing regimens could be more effective than imipenem/clavulanate-containing regimens. This information can guide clinicians in choosing the most effective treatment options, potentially leading to higher sputum culture conversion rates and better overall treatment success. The similar safety profiles of both regimens also provides reassurance of the tolerability and safety of these treatments.

In **chapter 3**, the effectiveness and safety of meropenem/clavulanate-containing regimens in treating MDR- and XDR-TB is evaluated. The study included 264 patients, 96 treated with meropenem/clavulanate and 168 with meropenem/clavulanate-sparing regimens. The study reported that meropenem/clavulanate was effective in achieving sputum smear and culture conversion rates similar to those of the control group, despite the meropenem/clavulanate group having more severe disease and resistance to a larger number of drugs (one of the reasons why meropenem/clavulanate was used). Adverse events were few and mainly gastrointestinal, further confirming the safety and tolerability of meropenem/clavulanate.

This chapter underscores the effectiveness and safety of meropenem/clavulanate-containing regimens in treating MDR- and XDR-TB, especially in challenging patients with severe disease and high drug resistance. For patients, this means that meropenem/clavulanate can be a viable treatment option that offers a good efficacy and safety profile. The findings support the use of meropenem/clavulanate as part of a comprehensive treatment plan DR TB.

In **chapter 4**, we compared the effectiveness and safety of imipenem/clavulanate added to an optimized background regimen (OBR) which at that time was a minimum of 20 months versus OBR control regimens in treating MDR- and XDR-TB. The study included 84 patients treated with imipenem/clavulanate-containing regimens and 168 controls treated with OBR alone. The results showed that imipenem/clavulanate-containing regimens achieved similar or lower sputum smear and culture conversion rates and treatment success rates compared to the control group. Adverse events were minor and infrequent, indicating that imipenem/clavulanate was well tolerated.

The results from this chapter indicate that adding imipenem/clavulanate to an optimized background regimen does not significantly improve treatment outcomes compared to the OBR alone. For patients, this suggests that while imipenem/clavulanate is well tolerated, it may not provide additional benefits over existing treatment regimens. This information can help clinicians make informed decisions about the inclusion of imipenem/clavulanate in treatment regimens.

In **chapter 5**, we present a case study of a person with XDR-TB who developed renal Fanconi syndrome while receiving a meropenem/amoxicillin-clavulanate-containing regimen. The patient experienced symptoms such as hypophosphatemia, metabolic acidosis, proteinuria, and glycosuria, consistent with generalized proximal tubular dysfunction. The condition improved upon discontinuation of the meropenem/amoxicillin-clavulanate regimen. This case calls attention to the potential for renal Fanconi syndrome as an adverse event associated with long-term use of meropenem/amoxicillin-clavulanate in treating DR-TB.

Clinicians can use this information to implement appropriate monitoring protocols and make timely adjustments to treatment regimens to ensure patient safety and to monitor patients for potential renal complications during treatment.

The combined findings from these chapters provide valuable insights into the effectiveness and safety of carbapenem-containing regimens for treating MDR- and XDR-TB. They highlight the potential benefits of meropenem/clavulanate and the need for careful

monitoring of adverse events. For people with XDR-TB, these insights could lead to more effective and safer treatment options, and lives saved.

PART 2, intensive care

In **chapter 6**, a systematic review of studies on the outcomes of people with pulmonary TB admitted to ICUs is provided. The review included 17 studies, with a total of 947 cases. The findings revealed that mortality rates for people with TB in ICU ranged from 29% to 95%, with a mean of 52.9%. The most common reason for ICU admission was acute respiratory failure. Negative predictors of outcome included hospital-acquired infections, the need for mechanical ventilation and vasopressors, delayed initiation of anti-TB treatment, multiple organ failure, and higher severity scores. The review also reported that existing severity scoring systems, such as APACHE II and SAPS II, often underestimate mortality in people with TB. The chapter emphasizes the need for earlier detection and treatment initiation to improve outcomes for people critically ill with TB.

In **chapter 7**, we report on a multicentric international observational study conducted by the International Severe TB and Rehabilitation Working Group of the Global Tuberculosis Network. The study included 434 TB patients aged over 15 years, admitted to ICUs across Europe, Asia, and Latin America from 2005 to 2018. Key findings include that over half of the patients were sputum smear-positive, and 85.7% were culture-positive. Most patients required invasive mechanical ventilation, vasopressor support, and steroids. Only 48.4% had TB medications initiated before or during ICU admission. The overall mortality rate was 54.8%, with 33.4% achieving treatment success.

Intravenous (IV) anti-TB drugs were administered to 43% of participants, with levofloxacin and amikacin being the most used. IV treatment lasting longer than 10 days was associated with better outcomes. IV rifampicin was linked to a lower mortality rate (35.7%) compared to those who did not receive it (51.7%).

We conclude that the high mortality rates seen in ICU TB patients necessitate improved management strategies. IV anti-TB drugs, particularly IV rifampicin, show potential benefits, suggesting the need for further prospective studies. Early screening and start of standardized treatment protocols could improve patient outcomes in high-incidence areas.

Overall significance

Chapters 6 and 7 provide critical insights into the management of people with TB in ICU settings. They highlight the high mortality rates associated with TB in critically ill people and the need for improved detection, treatment initiation, and management strategies. These findings suggest the potential benefits of IV anti-TB drugs and the importance of standardized treatment protocols to improve clinical outcomes. These insights are crucial for clinicians and healthcare providers in optimizing the care of people with TB in ICU settings.

General discussion and future direction on β-lactams

Relevance of beta-lactams/lactamases

β-lactams were dismissed as candidates for TB treatment soon after they were adopted as then found to be ineffective against *Mtb*. Only later was the mechanism understood to be due to rapid hydrolysis of the antimicrobials by BlaC, *Mtb's* chromosomally encoded, broad-spectrum β-lactamase. More recently, beta-lactamase inhibitors like clavulanate were discovered. These β-lactamase inhibitors irreversibly bind and deactivate BlaC.[1,2] After this finding, amoxicillin/clavulanate was used in combination with β-lactams in TB clinical trials and as a treatment option for DR-TB.[3-5] Unfortunately, clavulanate is not available on its own which requires physicians to use it with another combined β-lactam.[6-8] Some believe this leads to antagonism with competition between amoxicillin and the carbapenem at the penicillin binding protein site while others have postulated that amoxicillin may be synergistic in binding to a different site of the PBP.[9]

β-lactams are time dependent antimicrobials meaning that their activity increases proportionally with time that the concentration of the drug concentration remains above the MIC (T>MIC). The T>MIC of β-lactams is key to the pharmacodynamic anti-TB response.[10]

There are over a hundred individual β-lactam antimicrobials and their combinations with β-lactamase inhibitors, with new and repurposed formulations being developed to counter resistant infections. To date only amoxicillin, imipenem, meropenem, ertapenem, faropenem and sanfetrinem have been evaluated against *Mycobacterium tuberculosis* (Mtb) clinically.[11-13]

Currently available beta-lactams and combinations

The proof-of-concept for meropenem as an anti-TB drug was obtained with a 2-week early bactericidal activity (EBA) trial evaluating intravenous meropenem and amoxicillin/clavu-

lanate in people with pulmonary TB.[14] Meropenem was administered at a higher dose of 2 g three times daily (6 g total daily dose), in combination with oral amoxicillin/clavulanate (500/125 mg three times daily). There was an average daily fall in log10CFU of 0.11 and 0.17 for the meropenem-amoxicillin/clavulanate and HRZE arms respectively ($p<0.001$ for both groups, as compared with no effect; $p<0.001$ for the comparison between groups). A second EBA study evaluated the 14-day EBA of meropenem 6 g intravenously once daily administered over 6 hours with amoxicillin/clavulanate. There was an average daily fall in log10CFU of 0.094. Adverse events reported were mainly gastrointestinal and graded as mild.[15] This difference in activity in CFU between once daily dosing and thrice daily dosing of meropenem can be explained by the T>MIC.[16]

Regarding safety, the most frequent side effects reported from clinical trials and retrospective studies with meropenem include headache, nausea, constipation, diarrhoea, vomiting and skin rash (all above >2%).[17] Mild/moderate liver function abnormalities with mildly raised alanine transaminase can occur with long term intravenous use.[17] It has been reported that 50% of cases may resume treatment safely after brief cessation; however should transaminases rise again significantly then the β-lactams should be stopped indefinitely.[7] Use of broad-spectrum agents and the need of a central venous line increase the likelihood of line associated infections, commonly candidemia and gram-negative blood stream infections.[8] All β-lactams can cause potential adverse events such as rashes, allergic reaction, and anaphylaxis, however people allergic to penicillin rarely (<1%) have cross reactivity with carbapenems and these may be given safely with caution as long as they are not also allergic to cephalosporins.[18,19]

Our group utilised meropenem, imipenem and ertapenem as part of multi-drug regimens to treat patients with MDR-TB and XDR-TB in Italy.[20-23] The safety, tolerability, and efficacy of meropenem, imipenem and ertapenem were retrospectively collected from MDR/XDR-TB cases treated at a sanatorium between 2008 and 2015, all carbapenems were well tolerated.[20-25] Adverse events were few but mainly gastrointestinal. Drug induced liver injury was not infrequent and led to the frequent suspension of liver toxic drugs. Of note on further administration of the carbapenem, transaminases remained normal in half of cases and therefore can be continued in some cases.[26] Several cases of line associated candidemias with the use of these agents occurred, this is probably due to selection of candida in the GI tract and skin that can colonise then infect vascular lines used for longterm administration of intravenous carbapenems and cause systemic infection.[27]

Repurposing of an available oral β-lactam compound could be a solution to the challenges faced by intravenous administration of anti TB drugs.[28] Firstly, oral drugs can be taken at home, secondly do not require vascular lines and several daily administrations with the risk of line related infections, thirdly are probably cheaper than hospitalisation, fourth an oral drug could be adopted by TB programs and impact a larger number of people affected by TB. Oral carbapenems like tebipenem and sanfetrinem are currently in development and may offer effective, bioavailable, and actively bactericidal options for TB treatment possibly without the need for adjunctive amoxicillin/clavulanate.[28-33]

New developments

The repurposing of β-lactam antibiotics for TB treatment has gained renewed interest, largely catalyzed by the pioneering work of Hugonnet and colleagues.[1] Their research demonstrated that IV carbapenems could be effectively used to treat DR-TB cases, leading to their incorporation into salvage regimens. However, the limitations of IV administration and the need for more accessible treatment options prompted a broader search for orally bioavailable β-lactams with activity against Mtb. This effort was notably advanced by Gold et al., who led a large-scale collaborative initiative involving multiple pharmaceutical companies (GSK, Sanofi, Lilly, and MSD) and academic institutions.[34] Their goal was to identify β-lactam antibiotics with potent anti-Mtb activity.

Contrary to belief at the time, Gold and colleagues discovered that close to a fifth of the 8,900 β-lactam compounds screened exhibited significant activity against Mtb, with several demonstrating efficacy in murine infection models. Following initial hit confirmation and secondary assays, the pool was narrowed to 1,968 compounds, which were resupplied and tested for their minimum inhibitory concentrations (MIC90) under both replicating and non-replicating conditions. Clavulanate dependency testing was then conducted on 418 compounds, revealing that 11.7% exhibited a ≥4-fold increase in potency in the presence of clavulanate. From this refined group, 48 β-lactams were selected for further pharmacokinetic (PK), drug metabolism and pharmacokinetics (DMPK), chemical, and phenotypic profiling. Selection criteria were based on compound activity, availability, purity, and stability. Amongst the most promising candidates, the cephalosporin TBBL-0000316 demonstrated in vivo efficacy in Mtb-infected mice. This initiative was a good example of a successful public-private collaboration, allowing for the sharing of proprietary compounds and data to facilitate a comprehensive evaluation of β-lactam efficacy. The screening revealed a diverse array of β-lactams, with cephalosporins emerging as particularly promising. The study showed the therapeutic potential of β-lactams in TB treatment, especially in the

context of rising antimicrobial resistance, and also the requirement for further optimization of lead compounds, in particular to PK and bioavailability.[34]

Sanfetrinem cilexetil emerged as a particularly promising candidate through this high throughput screening. It demonstrated potent intracellular and extracellular activity against Mtb, with enhanced efficacy in cholesterol-based media that better mimic in vivo conditions. Sanfetrinem was active against drug-susceptible, MDR, and XDR clinical isolates. In vitro studies revealed rapid bactericidal activity, a significant post-antibiotic effect, and strong synergy with amoxicillin, rifampicin, rifapentine, and ethambutol. In vivo efficacy was confirmed using DHP-1 knockout mice, which more accurately model human β-lactam pharmacokinetics. Sanfetrinem significantly reduced lung bacterial burden, with efficacy comparable to meropenem-based regimens.[29] Its oral bioavailability and broad-spectrum activity have led to its advancement into a phase 2a clinical trial in South Africa (NCT05388448).[30]

In parallel, Quan et al. conducted a focused evaluation of seven β-lactams (cefadroxil, tebipenem, cephradine, cephalexin, cefdinir, penicillin V, and flucloxacillin), two β-lactamase inhibitors (avibactam and clavulanate), and three second-line TB drugs (moxifloxacin, levofloxacin, and linezolid).[35] Compounds were selected based on inhibitory concentration, oral bioavailability, and commercial availability. Cefadroxil and cephalexin emerged as the most promising cephalosporin, demonstrating strong synergistic effects when combined with clavulanate and other β-lactams. Clavulanate significantly enhanced β-lactam activity compared to avibactam, leading to its exclusive use in subsequent investigations. Several β-lactam combinations showed synergistic effects particularly those containing cefadroxil and cephalexin. Combinations with second-line TB drugs such as moxifloxacin and linezolid often resulted in antagonistic interactions. Quan et al. emphasized the potential of β-lactam synergy to support effective combination therapies for TB and advocate for further clinical evaluation of these regimens. Their findings reinforce the importance of repurposing existing antibiotics to address the growing challenge of drug-resistant TB and to expand the therapeutic arsenal.[35]

A complementary approach by Negatu et al. explored the use of dual β-lactam combinations to enhance TB treatment.[36] While this strategy has shown success against non-tuberculous mycobacteria, it had not previously been applied to Mtb, despite similarities in peptidoglycan synthesis. The study identified cefuroxime as a potent enhancer of the bactericidal activity of tebipenem, sulopenem, and amoxicillin. The combination of these agents achieved effective bactericidal activity at lower concentrations than when used individually, suggesting the

potential to shorten TB treatment duration. Screening of various oral β-lactam pairs revealed that combinations such as tebipenem-clavulanate and sulopenem-cefuroxime significantly reduced bacterial load in vitro.[36]

Together, these studies reflect a growing consensus on the potential of β-lactams in combination regimens, as viable therapeutic options for TB. Remaining knowledge gaps and little investment in β-lactams for TB treatment however remain.[36-38] Ongoing research may soon inform whether these newer β-lactam agents are sufficiently bioavailable, concentrate sufficiently in the target organ particulalerly lungs and intralesionally within granulomas and are actively bactericidal without the need for adjunctive amoxicillin/clavulanic acid. However, several challenges remain, some of which have been previously highlighted.

One such concern is the unregulated marketing and widespread use of oral penems which has already been seen with generic faropenem sodium, which may inadvertently contribute to the rise of carbapenem resistance and antibiotic misuse. It is clear that antimicrobial stewardship is key with these drugs.[39,40]

An example of dysregulated use and risk of antimicrobial resistance is faropenem. Faropenem garnered attention due to its stability against β-lactamases and its broad-spectrum efficacy, particularly against extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*. It is commonly used to treat respiratory, urinary tract, and skin infections. Unlike meropenem, which requires co-administration with a β-lactamase inhibitor, faropenem in vitro demonstrates intrinsic activity against *Mycobacterium tuberculosis*, including MDR and XDR strains. It efficiently inactivates Mtb L,D-transpeptidases and exhibits greater resistance to β-lactamase hydrolysis than meropenem. However, despite its promising biochemical profile, two phase IIa trials evaluating the early bactericidal activity of oral faropenem against Mtb yielded disappointing results. These findings, coupled with its widespread community use in Asia, suggest that faropenem's efficacy in TB may be compromised and could potentially limit the effectiveness of other repurposed or future β-lactam agents.[39,41]

Global regulatory oversight is essential to prevent the misuse of oral penems and intravenous carbapenems and to preserve the utility of β-lactams in TB treatment. These considerations are likely to apply to any future cephalosporin or carbapenem developed for TB. As such, coordinated international efforts are needed to combat antimicrobial resistance and to safeguard the effectiveness of these critical therapeutic agents.[39,40]

Knowledge gaps about beta-lactams in TB

Despite growing interest in β-lactams for TB, several important knowledge gaps remain. The PK/PD of β-lactams in TB though dependent on T/MIC lack therapeutic drug monitoring targets to ensure adequate drug exposure.[42] As broad-spectrum antibiotics, β-lactams can disrupt the host microbiome, potentially leading to gastrointestinal side effects, most commonly mild to moderate diarrhoea. However, the severity, frequency, persistence, and overall impact on the microbiome in TB patients require further investigation.[43] Additionally, β-lactam use may exert selective pressure on other host bacteria, potentially promoting antimicrobial resistance in organisms such as *Enterobacteriaceae*, *methicillin-resistant Staphylococcus aureus* (MRSA), *Clostridioides difficile* and *Candida* species.[44] These concerns are particularly relevant when considering broad-spectrum antimicrobial therapy outside of salvage regimens. Antimicrobial surveillance as well as antimicrobial stewardship could help mitigate some of the risks regarding development of resistance through increased β-lactam use in TB programs.[40,45] However it is highly likely that the use of broad spectrum antimicrobials will increase the risk of selection of resistant pathogens and moulds in patients and contribute to greater antimicrobial resistance within the community. In the VQUIN trial the effect of moxifloxacin on faecal flora of people with latent TB infection was assessed.[46] It is likely that similar assessments will be required for any future β-lactam used for people with TB. Repurposed drugs like cefodroxil, cephaelxin or oral penems currently in development like sanfetrinem and tebipenem may hold the key to bringing well tolerated oral drugs to the TB clinic, however studies are needed.[28,47] The absence of an oral drug, a requirement outlined in the WHOs target regimen profiles,[48] currently allocates β-lactams (intravenous meropenem) for people with limited therapeutic options like extensively drug-resistant TB.[49]

General discussion of TB treatment in the ICU

Challenges of TB on the ICU

The higher mortality rates associated with TB, especially among critically ill people in Intensive Care Units (ICUs), behooves us to consider the need for more effective drugs and treatment strategies.[50-52]

Critically ill people often face challenges related to drug absorption and thus exposure due to altered physiological conditions, including impaired gut motility, and organ dysfunction. IV administration could ensure that therapeutic drug levels are rapidly achieved, which is

crucial for effective bacterial clearance and reducing bacillary loads.[52-54] This is particularly important in severe TB cases, where rapid and effective treatment can make a significant difference in clinical outcomes.[55]

Existing data

Our retrospective observational study provides valuable insights into the potential benefits of IV anti-TB treatments in an intensive care setting. This study conducted by the *Global Tuberculosis Network* concluded that high mortality rates in ICU TB patients require improved management strategies. IV anti-TB drugs, particularly IV rifampicin, showed potential benefit, advocating for further prospective studies. Early screening and start of standardized treatment could improve outcomes in high-incidence areas.[56]

Availability of drugs and formulations

However, the study also highlighted variability in resources, treatment protocols and the availability of IV anti-TB drugs across different regions, and these have been further affected from COVID-19 and conflicts. Findings suggest that regions with better access to IV rifampicin, such as Hong Kong, experienced lower mortality rates compared to regions with limited access, such as Latin America. This disparity calls for standardized treatment protocols and improved access to IV anti-TB drugs in resource-limited settings, and drug access resilience to counter frequent stock outs.[57-61]

Limitations

Clinical challenge is the long duration before being able to appreciate an effect with treatment, likely the delay in diagnosis leads to severe forms which later either lead to poor outcome or slow improvement with treatment, earlier diagnosis and better treatment response biomarkers are needed. Our study's retrospective design and the heterogeneity of the patient population are further important limitations.[56] The variability in treatment protocols, duration, dosage and availability of IV drugs, as well as the differing levels of resource and healthcare infrastructure across regions, are likely to have influenced the outcomes and created noise. Additionally, the lack of therapeutic drug monitoring at most sites further complicates the interpretation of the findings.[56]

Despite these limitations, the ICU study provides important evidence supporting the potential benefits of IV anti-TB drugs in managing people critically ill with TB.[56] Future prospective studies are needed to confirm these findings and establish standardized guidelines for the use of IV anti-TB drugs in ICU settings. Early screening, timely initiation of treatment,

and the use of higher doses or IV administration of first-line anti-TB drugs could improve outcomes and reduce the high mortality associated with TB in this setting.[62]

Future directions

Given the high mortality and toxicity associated with TB in intensive care units (ICUs), the frequent delays in initiating anti-TB therapy, and the practical challenges or impossibility of administering IV medications in critically ill patients, several alternative strategies warrant exploration.[62] One promising direction is the development of oral carbapenems for TB and other infections, which could help overcome the logistical and clinical barriers posed by continuous IV administration and allow for a stepdown from IV therapy. These agents may offer a more feasible route of delivery in resource-limited settings, while retaining the efficacy needed for treating DR TB.[63] Ideally oral TB treatment with a food effect should no longer be crushed and added to feed via nasogastric tubes so access to new formulations including IV formulations may be of benefit for people with TB in intensive care. People with TB should not be denied access to intensive care due to their diagnosis.

Conclusion

In summary, the high mortality rate among people with TB in ICU settings, calls attention to the need for improved treatment strategies. Extended IV treatment, particularly with drugs like IV rifampicin, might lead to better patient outcomes. The advantages of IV administration, which ensures rapid achievement of therapeutic drug levels crucial for effective bacterial clearance, are evident. However, variability in treatment protocols and the availability of IV drugs across different regions of the globe highlight the need for standardized treatment protocols and improved access, particularly in resource-limited settings. β-lactams, especially when combined with β-lactamase inhibitors like clavulanate, may present a promising avenue for treating drug-resistant TB. To consolidate these findings, prospective studies are essential to establish comprehensive guidelines for IV anti-TB drug use in ICU settings. Additionally, early screening and importantly timely initiation of treatment are critical for improving patient outcomes.

Oral carbapenems are in development for TB and other infections, representing an opportunity towards achieving this goal. One such carbapenem, tebipenem, is in late stages of development, and sanfetrinem, a member of a novel class of tricyclic carbapenem antibiotics, is currently in a phase 2 EBA study. These new agents may soon offer sufficiently bioavailable and actively bactericidal options without the need for adjunctive amoxicillin/

clavulanate. Furthermore the possibility to repurpose commercially available cephalosporins offers hope for more accessible, effective, and convenient TB treatment options, potentially transforming the landscape of drug-resistant TB management globally.

Remaining knowledge gaps

The pharmacokinetics and pharmacodynamics (PK/PD) of β-lactams in TB are not sufficiently clear to ensure adequate exposures and tissue distribution, and therefore further studies and tools are needed.

β-lactams are broad-spectrum and impact the host's microbiome, potentially causing gastrointestinal events, and so selective compounds that do not affect flora to a lesser extent and contribute to antimicrobial resistance are needed.

An oral, once- or twice-daily dosed carbapenem treatment would be accessible for outpatients, benefiting the majority of people suffering from TB worldwide. This approach could reduce the need for hospitalization, lower the risk of line-related infections, and make treatment more cost effective and widely used by TB programs.

Future perspectives

- Conduct prospective studies: to confirm or refute the findings of the retrospective observational studies and establish standardized guidelines for the use of IV anti-TB drugs in ICU settings.
- Develop oral β-lactams for TB: continue the development and clinical trials of new or repurposed oral carbapenems and cephalosporins with respective β-lactamase inhibitors.
- Evaluate PK/PD: conduct detailed studies on the pharmacokinetics and pharmacodynamics of β-lactams in TB to ensure adequate exposures and tissue distribution.
- Monitor resistance: implement strategies to monitor and mitigate the development of antimicrobial resistance due to the use of broad-spectrum β-lactams.
- Standardize protocols: develop and disseminate standardized treatment protocols for the use of IV treatment in the ICU and oral β-lactams in TB treatment, that are compatible with resource limited settings.
- Early screening and treatment: emphasise the importance of early screening and timely initiation of treatment through standardized protocols including empirical TB treatment in ICU settings in high prevalence areas to improve outcomes.

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Chapter 11

From clinic to hopefully find a better cure: a clinician's journey into translational medicine and TB drug development

I began my career as an infectious disease specialist, treating patients in a busy HIV clinic and trial centre in Milan. There I was encouraged to be the sub-investigator in several HIV drug clinical trials, including drugs like atazanavir/ritonavir, lopinavir/ritonavir and lamivudine monotherapy as a strategy to select for the E184V mutation to decrease viral fitness and give people living with a HIV up to a 6 month break from treatment and spare them significant side effects from protease inhibitors. In Africa while on a clinical attachment treating people in the medical wards in two Ugandan hospitals, I was frustrated by the number of people dying from tuberculosis. I also encountered several cases of drug-resistant Tuberculosis who were being treated with repeated cycles of first line drugs as there was no other alternative at that time. On my return to Italy I worked at the National TB Reference centre in Sondalo and encountered case after case of drug-resistant tuberculosis (TB). We were increasingly frustrated by the limitations of existing treatments and the need for surgery and intravenous drugs during long in hospital stays. We repurposed several drugs like linezolid, imipenem, ertapenem and meropenem and documented the results in retrospective studies. Determined to make a broader impact, I left Sondalo for London where I worked in general Infectious diseases and had the opportunity to set my sights beyond the clinic with Queen Mary University working on numerous observational studies and establishing a postgraduate TB certificate course. With the advent of COVID-19 I went back into drug trials and refound my mojo evaluating dexamethasone, tocilizumab, baricitinib, casirivimab and imdevimab which were effective and azithromycin, hydroxychloroquine, lopinavir-ritonavir, convalescent plasma, colchicine, aspirin, dimethyl fumarate which were found not to be effective. I have now joined GSK to develop new TB drugs to continue working in clinical trials and work on my dream of developing an oral carbapenem for TB.

Facing barriers and building bridges

Despite my passion and drive, I have faced significant challenges. Balancing patient care, research and family has been exhausting, burning a candle from both ends unfortunately being unsuccessful in negotiating protected research time and obtaining institutional support necessary to maintain my clinical responsibilities while advancing research.

At GSK however I have managed to find time to develop both clinical and research pursuits, splitting my time in the TB and NTM clinics and clinical trials. Developing new TB drugs is exhilarating but a long process requiring several studies, large teams of highly dedicated people working together and several milestones to cross. TB lacks the commercial appeal of other diseases and this unfortunately prolongs and complicates development.

Strategic solutions

I am working in multiple avenues to overcome constraints and barriers of drug development through:

- Collaborations: partnering with academic institutions, other pharmaceutical companies, and non-profits. These consortia provide access to resources, expertise, and shared goals and possibly cheaper studies through pooling of resource and applying for funding together.
- Data sharing: joining and co-leading a group looking at and sharing data amongst consortia and leveraging global contributions to accelerate progress.
- Efficient esearch: I work with others using models and AI to identify promising regimens before moving to costly trials.
- My aspiration is to develop a new oral B-lactam that can show promise against multidrug-resistant TB. Furthermore I am working to help create shorter, safer, better tolerated drug regimens for TB, bringing treatment down to weeks rather than months, evaluating novel modes of administration like long acting injectables to truly revolutionise the field. The dream would be to be able to dose a potent oral regimen for 2-8 weeks followed by a long-acting injectable formulation that will replace the current continuation phase of 4 months. Though we are still in early clinical trials, the drugs and their regimens represent hope to people with tuberculosis.

I continue to see patients, teach students, and guide pharmaceutical collaborations. My journey from bedside to benchside and keeping the patient at the centre of the process demonstrates how clinicians can drive meaningful change, even in the face of challenges.

Chapter 12

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Appendices

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List of abbreviations

AIDS	Acquired Immunodeficiency Syndrome
APACHE II	Acute Physiology And Chronic Health Evaluation II
ARDS	Acute Respiratory Distress Syndrome
BCG	Bacillus Calmette–Guérin
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
DILI	Drug-Induced Liver Injury
DR-TB	Drug-Resistant Tuberculosis
DST	Drug Susceptibility Testing
EBA	Early Bactericidal Activity
ESBL	Extended-Spectrum Beta-Lactamase
HAI	Hospital-Acquired Infection
HIV	Human Immunodeficiency Virus
HRZE	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol
ICU	Intensive Care Unit
IQR	Interquartile Range
IV	Intravenous
MDR-TB	Multidrug-Resistant Tuberculosis
MIC	Minimum Inhibitory Concentration
MOF	Multi-Organ Failure
NTM	Non-Tuberculous Mycobacteria
OBR	Optimized Background Regimen
OR	Odds Ratio
PK/PD	Pharmacokinetics/Pharmacodynamics
RR-TB	Rifampicin-Resistant Tuberculosis
SAPS II	Simplified Acute Physiology Score II
SOFA	Sequential Organ Failure Assessment
TB	Tuberculosis
XDR-TB	Extensively Drug-Resistant Tuberculosis

About the author



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Simon is a Global Health Physician at GSK and Honorary Clinical Professor in Infectious Diseases at Barts Health NHS Trust and Queen Mary University of London. He practices at several TB clinics in London.

He is vice chair of the Global TB Network Consilium and co-chair of the Queen Mary University of London postgraduate TB certificate programme. He is member of the WHO European Research initiative.

His interests focus on Mycobacteria, and respiratory infections. He is currently involved in a number of clinical trials developing new TB drugs.

He is deputy editor of the IJTLD and program officer for the TB section of the UNION.

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