Evaluation of carbapenems for multi/extensive-drug resistant *Mycobacterium tuberculosis* treatment

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Abstract

M/XDR-TB has become an increasing threat in high burden countries but also in affluent regions due to increased international travel and globalization. Carbapenems are earmarked as potentially active drugs for the treatment of *M. tuberculosis*. To better understand the potential of carbapenems for the treatment of M/XDR-TB, the aim of this review was to evaluate the literature on currently available *in vitro*, *in vivo* and clinical data on carbapenems in the treatment of *M. tuberculosis* and detection of knowledge gaps, in order to target future research.

In February 2018, a systematic literature search of PubMed and Web of Science was performed. Overall the results of the studies identified in this review, which used a variety of carbapenem susceptibility tests on clinical and lab strains of *M. tuberculosis*, are consistent. *In vitro* the activity of carbapenems against *M. tuberculosis* is increased when used in combination with clavulanate, a BLaC inhibitor. However, clavulanate is not commercially available alone, and therefore is it practically impossible to prescribe carbapenems in combination with clavulanate at this time. Few *in vivo* studies have been performed, one prospective, two observational and seven retrospective clinical studies to assess effectiveness, safety and tolerability of three different carbapenems (imipenem, meropenem and ertapenem). Presently we found no clear evidence to select one particular carbapenem among the different candidate compounds, to design an effective M/XDR-TB regimen. Therefore more clinical evidence and dose optimization substantiated by hollow fiber infection studies are needed to support repurposing carbapenems for the treatment of M/XDR-TB.
Treatment of tuberculosis (TB), a disease caused by *Mycobacterium tuberculosis*, has become more challenging with the emergence of multidrug resistant (MDR)-TB and extensively drug resistant (XDR)-TB among previously and newly detected cases (1). M/XDR-TB has become an increasing threat in high burden countries but also in affluent regions due to increased international travel and globalization.

MDR-TB is defined as an infectious disease caused by *M. tuberculosis* that is resistant to at least isoniazid and rifampicin. XDR-TB is defined as MDR-TB with additional resistance to at least one of the fluoroquinolones and to at least one of the injectable second line drugs (amikacin, capreomycin or kanamycin). New TB drugs, with a novel mechanism of action, include bedaquiline and delamanid that have recently been approved and included in the World Health Organization guidelines on MDR-TB as add-on agents (2). Unfortunately resistance to these agents has already been detected (3).

Exploration of currently available drugs for their potential effect against TB, may be an additional source for potential candidates to be used in case of extensive resistance to try to compose a treatment regimen (4-5).

Beta-lactam antimicrobial drugs are widely used drugs for the treatment of a range of infections. Also, imipenem-cilastatin and meropenem have been listed as add-on drugs in the updated WHO treatment guidelines (6). Carbapenem activity has long been considered to be of limited use, due to rapid hydrolysis of the beta-lactam ring by broad-spectrum mycobacterial class A beta-lactamases (BLaC). The addition of the BLaC inhibitor clavulanate suggests that beta-lactams combined with BLaC inhibitors could be beneficial in the treatment of TB (7). Recent studies suggest that beta-lactams, using clavulanate/clavulanic acid, show more activity against *M. tuberculosis*(7-14).
The bacterial activity of beta-lactams is due to the inactivation of bacterial transpeptidases, commonly known as penicillin binding proteins (PBP), which inhibit the biosynthesis of the peptidoglycan layer of the cell wall of bacteria \((8,15)\). Polymerizations of the peptidoglycan layer in most bacteria are predominantly cross-linked by D,D-transpeptidases (DDT), the enzymes inhibited by beta-lactams \((8,16)\). The majority of crosslinks in peptidoglycan appear to be formed by the non-classical L,D-transpeptidases (LDT) in \(M.\) \textit{tuberculosis} \((17-23)\). Several studies revealed the structural basis and the inactivation mechanism of LDT and the active role of carbapenems, providing a basis for the potential use of carbapenems in inhibiting \(M.\) \textit{tuberculosis} \((24-28)\).

Beta-lactams show time-dependent activity, carbapenems have been shown to have bactericidal activity when the free drug plasma concentration exceeds the MIC for at least 40% of the time in non-TB bacterial species \((29-30)\).

Carbapenems are earmarked as potentially active drugs for the treatment of \(M.\) \textit{tuberculosis}. To better understand the potential of carbapenems for the treatment of M/XDR-TB, the aim of this review was to evaluate the literature on currently available \textit{in vitro}, \textit{in vivo} and clinical data on carbapenems in the treatment of \(M.\) \textit{tuberculosis} and detection of knowledge gaps, in order to target future research.
Methods

Prisma

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (31).

Search

In February 2018, a systematic literature search of PubMed and Web of Science, without restrictions with respect to publication date was employed using the key words (‘Carbapenem’ OR ‘Carbapenems’ OR ‘Imipenem’ OR ‘Meropenem’ OR ‘Ertapenem’ OR ‘Doripenem’ OR ‘Faropenem’ OR ‘Biapenem’ OR ‘Panipenem’ OR ‘Tebipenem’) AND (‘Tuberculosis’ OR TB OR Mycobacterium tuberculosis) as MeSh Terms. Retrieved studies and abstracts from both PubMed and Web of Science were pooled and duplicates were removed. Titles and abstracts of retrieved articles were screened. Reviews, case-reports or studies on other species than TB or studies on other drugs than carbapenems were excluded. Studies were screened for eligibility. If eligible, the full-text was read by a researcher (SvR). A second researcher (MZ) independently repeated the article search and selection. Discrepancies were resolved by discussion, or a third researcher was consulted (JWA). Full text papers were subdivided into three sections; in vitro, in vivo and clinical data. Full text papers for in vitro data were eligible for inclusion if an M. tuberculosis strain was studied and minimum inhibitory concentrations were reported. Full text papers for in vivo data were eligible for inclusion if treatment of M. tuberculosis infections with carbapenems were studied in animal models, and if colony forming units and/or survival data were reported. Full text papers for clinical data were eligible for inclusion if pharmacokinetics of carbapenems or safety or response to treatment measured as surrogate end points (sputum conversion) or clinical end points were studied and reported. References of all included articles were screened by hand. The same systematic search was performed using clinicaltrials.gov to find ongoing studies investigating carbapenems in TB patients (Feb 2018).
A researcher (SvR) performed data extraction first by using a structured data collection form. A second researcher (MZ) verified the data extraction independently. Data were subdivided into three sections; in vitro, in vivo and clinical data. Variables in the section ‘in vitro’ included; *M. tuberculosis* strain, experimental methods, drug of interest. Minimal inhibitory concentration, minimal inhibitory concentration with clavulanic acid, minimal bactericidal concentration and colony forming units (CFU) were extracted from the included articles. For the section ‘in vivo’ the following data were included; *M. tuberculosis* strain, mice, route of infection, drug of interest with or without clavulanic acid, dose, and treatment, colony forming units and survival rate, were retrieved from the included articles. For the clinical section, we extracted data from the included articles on type of study population, number of subjects, study design, drug of interest, and dosage. Sputum smear, sputum culture, treatment success, adverse events and interruption due to adverse events were noted as outcomes. AUC, Peak drug concentration ($C_{\text{max}}$), half-life ($t_{1/2}$), Distribution volume (Vd), and clearance were extracted. Possibility of pooling data from included data was assessed on data presentation.

**Data quality**

No validated tool for risk of bias assessment for in vitro studies, in vivo studies and pharmacokinetic studies was available. To be able to assess the quality of each study, we verified if each study reported on key-elements required for adequate data interpretation. If studies reported adequately on the key-elements, risk of bias was considered to be low. If studies had missing data or if procedures were not clear or not mentioned, risk of bias was considered to be high. The following key-elements were identified for in vitro studies; description of lab or clinical strains, minimal sample size of >10 strains, >3 concentrations tested per drug, MIC/CFU determined using the proportion method, evaluation endpoint of minimal inhibitory concentration (MIC 50 or MIC 90), evaluation of endpoint of minimal bactericidal concentration (MBC99) and CFU reduction, for in vivo studies;
description of laboratory or clinical strains, type of mice, route of administration of the drug, dose and treatment duration, MIC/CFU determined using the proportion method, evaluation of endpoint of CFU and survival rate and for clinical studies; for human studies; study design, patient population (TB/MDR-TB; HIV co-infection), number of study participants, endpoints tested, defined as sputum smear conversion, sputum culture conversion, treatment success, adverse events. The following components were checked for pharmacokinetic studies: sample size, type of patients, type of assay, number of plasma samples drawn per patient, sample handling, use of validated analytical methods and method of AUC calculation.

Results

Based on the selection criteria, 250 articles were retrieved in PubMed and 260 in Web of Science. After removal of 146 duplicates, 364 articles remained for screening. After screening of the title and abstract, 46 articles remained for full text evaluation. Reasons for exclusion included; not available (n=6), other drugs (n=2), no MIC (n=1), case-report (n=1), other (n=1). After this process, 35 relevant articles were included in this study (Flow chart; Fig 1). Due to low number and high diversity of strains, analytical methods and study designs, presence of biochemical instability of the drugs of interest, the short half-life of drugs of interest in mice and the diversity in MIC determination, we did not have enough data to perform a meta-analysis. Risk of bias of the included studies is shown in table S1. Studies on clinicaltrials.gov are shown in S2.

In vitro

Results of the in vitro studies reporting on carbapenems are presented in table 1.

Imipenem

Susceptibility testing of imipenem, using various analytical methods against strain H37Rv, H37Ra, Erdman and clinical isolates of M. tuberculosis showed a range of MIC’s between 2 – 32 mg/L
without clavulanic acid and a range of MIC’s between 0.16 – 32 with clavulanic acid. (8,32-37). When Imipenem was combined with clavulanate it showed a 4-16-fold lower MIC against the *M. tuberculosis* H37Rv reference strain (8,33-35).

**Meropenem**

Multiple studies reported that meropenem in presence of clavulanate is active *in vitro* against clinical and lab strains, H37Rv and H37Ra, of *M. tuberculosis*, showing MIC’s ≤ 1 mg/L. *In vitro* studies reporting susceptibility of meropenem of *M. tuberculosis* reference strain and clinical isolates showed MIC values between 1 - 32 mg/L (8,33-44). Meropenem in combination with clavulanic acid was shown to have a MIC between 0.063 – 32 mg/L (33-35,38,43) Meropenem in combination with clavulanate killed the non-replicating ss18b strain of *M. tuberculosis* moderately and was shown to have a MIC of 0.125 – 2.56 mg/L against *M. tuberculosis* H37Rv strains (8,34-35,40). A decrease of a 2 log10 CFUs over six days was reported in *M. tuberculosis*-infected murine macrophages (40).

**Ertapenem**

In clinical strains of *M. tuberculosis* the MIC of ertapenem, as single agent, was 16 mg/L and when combined with clavulanate 4 mg/L (33,35). Another study showed ertapenem was unstable degrading faster than the doubling time of *M. tuberculosis* in the growth media used, suggesting previous published MICs of ertapenem are likely to be falsely high (45). In a hollow fiber model with supplementation of ertapenem in a broth microdilution test, ertapenem showed a MIC of 0.6 ml/L (46). A 28-day exposure-response hollow fiber model of TB study tested 8 different doses of ertapenem in combination with clavulanate and identified the ertapenem exposure associated with optimal sterilizing effect for clinical use. Monte Carlo simulation with 10,000 MDR-TB patients identified a susceptibility breakpoint MIC of 2 mg/L for an intravenous dose of 2 g once a day that achieved or exceeded 40%T>MIC. (46)

**Faropenem**
Faropenem showed a 4-fold reduction when combined with clavulanic acid \((33,34)\), resulting in a MIC range between 1 - 5 mg/L \((33,34, 47-49)\). In a hollow fiber model, the optimal target exposure was identified to be associated with optimal efficacy in children with disseminated TB using Monte Carlo simulations; the predicted optimal oral dose was 30 mg/kg of Faropenem/medoximil 3-4 times daily.

The exposure target for Faropenem/medoximil was 60% \(T_{\text{free}}\geq MIC\) \((50)\).

**Other carbapenems**

Other carbapenems, such as doripenem, biapenem and tebipenem showed at least a 2-fold reduction in MIC when combined with clavulanic acid \((33,37,43, 51)\).

**In vivo**

Results of the *in vivo* studies reporting on carbapenems are presented in table 2.

**Imipenem**

The bacterial burden in imipenem-treated CD-1 female mice (twice daily (BID) 100 mg/kg), infected with *M. tuberculosis* strain H37Rv, was reduced by 1.8 log10 in splenic tissue and 1.2 log10 in lung tissue after 28 days, showing an anti-mycobacterial effect as well as improved survival in this mouse model \((52)\). In another study Swiss mice, infected with *M. tuberculosis* strain H37Rv, were treated with a subcutaneous administration of 100-mg/kg imipenem in combination with clavulanate once a day to simulate a human equivalent dose. The CFU count after 28 days of treatment increased compared to the CFU count at start of treatment. There only was a significant difference in the imipenem-clavulanlate treated mice \((35)\).

**Meropenem**

It has been reported that 300 mg/kg BID meropenem alone, and in combination with 50 mg/kg clavulanate both resulted in a significant, though modest reduction, in CFUs in lung and spleen.
tissues in C57BL/6 mice (40). Veziris et al. reported a CFU increase compared to start of the treatment of meropenem when given as mono-therapy or in combination with clavulanate in a dose of 100 mg/kg, on CFUs, spleen weights, or lung lesions in Swiss mice (35). Meropenem in a dose of 300 mg/kg in combination with clavulanate, 75 mg/kg thrice-daily given to BALB/c mice showed marginal reduction in CFU counts in the acute model and no reduction in the chronic model (34). Meropenem, given subcutaneously 300 mg/kg three times a day, showed a CFU count reduction of 1.7 log in the lungs of TF3157 DHP-1 deficient mice. (53)

Ertapenem

In a murine TB model infected with H37Rv, a dose of 100 mg/kg once daily ertapenem as monotherapy or in combination with clavulanate had neither bactericidal nor bacteriostatic activity in lungs and spleens of TB-infected mice. Spleen weight and lung lesions remained similar compared to the untreated group of mice. There was an increase in CFUs compared to the CFUs at the start of the treatment (35).

Other Carbapenems

An oral dose of 500 mg/kg Faropenem medoxil, given three times daily, gave a reduction of 2 log CFU count in the lungs of TF3157 DHP-1 deficient mice (53). Neither in vivo nor clinical studies for other carbapenems as part of a multi-drug regimen against TB were retrieved.

Clinical studies

Results of the clinical studies reporting on carbapenems are presented in table 3.

Imipenem

Ten patients were treated with imipenem in combination with two or more other antimicrobial agents. It was reported that it was likely that 1g of imipenem (BID) contributed to sputum culture
conversion in these patients (52). A prospective study evaluated 1000 mg/day imipenem/clavulanate at a dose of once daily in 12 patients, 11 of these patients received linezolid-containing regimens. All patients showed sputum and culture conversion within 180 days. No adverse events were reported for imipenem/clavulanate (54). In a large observational study, the clinical outcomes of 84 patients, treated with 500 mg imipenem/clavulanate four times a day, were compared with results from 168 controls. The study showed that imipenem-containing regimens achieved comparable results compared to the imipenem sparing regimens, while success rates were similar to major international MDR-TB cohorts (55).

**Meropenem**

A regimen including meropenem-clavulanate given to 18 patients with severe pulmonary XDR-TB led to sputum culture conversion in 15 patients, of which 10 has successfully completed and five patients were considered cured according to WHO guidelines. Long-term safety was not a problem in this study as no adverse events were reported (56-57). The first study, that evaluated efficacy, safety and tolerability, was a case-control study in 37 patients, who received meropenem/clavulanate as part of a linezolid based multi-drug regimen. This is the first study that showed an added value of meropenem/clavulanate in a multi-drug regimen. The meropenem/clavulanate containing regimen showed a sputum microscopy conversion of 87.5 % and a sputum culture conversion of 83.8%, while the meropenem/clavulanate sparing regimen showed a sputum microscopy conversion of 56.3% and a sputum culture conversion of 62.5% after 90 days of treatment (58). In another study, 10 XDR and pre-XDR female patients were treated with multi-drug regimens and received meropenem/clavulanate for 6 months or more. Eight patients achieved sputum conversion after 6 months, while two patients died. (59). Pharmacokinetic parameters of 1 g meropenem/clavulanate given intravenously over 5 minutes showed a serum peak of 112 mg/ml and a concentration of 28.6 mg*h/L (39). In an observational retrospective cohort-study, efficacy and safety were evaluated in 96 patients treated with meropenem/clavulanate containing regimens and compared with 168 controls.
Sputum smear and culture conversion rates were found to be similar (60) in an observational study comparing therapeutic contribution, such as sputum smear and culture conversion rates and success rates, of imipenem/clavulanate and meropenem/ clavulanate in a background regimen, suggested that meropenem/clavulanate can contribute to the efficacy of a regimen in treating M/XDR-TB patients (11).

Ertapenem

The first report on clinical experience with ertapenem presented data from five patients who were treated with an intravenous injection of 1 g ertapenem once daily in a multi-drug regimen. Three of these patients showed sputum smear and culture conversion; four of five patients had a successful treatment outcome. Two patients interrupted treatment due to an adverse event. These adverse events were considered unrelated to the study drug (61). In an observational study 18 patients were treated with 1 g ertapenem once daily; fifteen of these patients had a successful treatment outcome were cured. Three patients were lost due to follow-up. Three patients stopped ertapenem treatment due to ertapenem unrelated adverse events. Pharmacokinetic parameters were evaluated in 12 patients, showing a mean peak plasma of 127.5 (range 73.9 - 277.9) mg /L and an AUC of 544.9 (range 390 - 1130) mg*h/L. Based on a MIC of 0.25 mg/ml 11/12 patients reached the target value of 40% Tfree>MIC was exceeded (10). The pharmacokinetic model composed in this study was shown to adequately predict ertapenem exposure in MDR-TB patients. The Monte Carlo simulation, which had a time restriction of 0–6 h, showed that the best performing limited sampling strategy was at 1 and 5 h after intravenous injection. (62). In another pharmacokinetic model study using prospective data from 12 TB patients it was observed that 2 g ertapenem once daily resulted in a more than a dose-proportional increase in AUC compared to once daily 1 g ertapenem. Based on a MIC of 1.0 mg/L, 11 out of 12 patients reached the target value of 40% Tfree>MIC (63).

Discussion
Hugonnet and colleagues first stated that carbapenems have antimycobacterial activity (7). Subsequently, studies addressing the inactivation mechanism of LDT provided the underlying evidence to support the hypothesis of activity of carbapenems against *M. tuberculosis* (14-28). In spite of this a series of *in vitro* studies have been carried out, some of which detected an effect and some of which did not (8,32-50). Only later, was it recognized that these confusing results are probably explained by the chemical instability of carbapenems, in culture media at the temperatures typically used in *in vitro* studies, and many previously published *in vitro* studies are likely to have reported falsely high MICs (45).

Overall the results of the studies identified in this review, which used a variety of experimental methods to test clinical and laboratory strains of *M. tuberculosis* for susceptibility to carbapenems, are consistent. Carbapenems are more active against *M. tuberculosis* if used in combination with clavulanate, a BLαC inhibitor. (8,32-50). In line with these *in vitro* studies the addition of clavulanate improved the survival rate in mice (35). As the European Medicines Agency (EMA) has accepted and qualified the *in vitro* hollow fiber system models as a methodology to define pharmacokinetic and pharmacodynamic (PK/PD) parameters, these modern *in vitro* studies can be used to avoid the problems associated with the chemical instability of these agents in standard agar based MIC testing. Thus, hollow fiber systems have the potential for dose finding and regimen selection studies on the use of carbapenems in the treatment of TB (64-65).

Few *in vivo* studies have been performed due to the short half-life and lower serum concentrations of carbapenems in mice (35).

One prospective, two observational and seven retrospective clinical studies to assess effectiveness, safety and tolerability of three different carbapenems (imipenem, meropenem and ertapenem) have been performed. Adverse events due to carbapenems were mild, confirming what we know from other infectious diseases; but in contrast to other repurposed drugs like linezolid (55,58,60). To date,
only two large retrospective studies with M/XDR-TB patients have been performed with imipenem (84 patients), and meropenem (96 patients) \(^{11}\). Meropenem/ clavulanate was suggested to be more efficient in managing M/XDR-TB \(^{11}\), however interpretational limitations were mentioned.

We found no clear evidence to select one particular carbapenem among the different candidate compounds, when designing an effective M/XDR-TB regimen. Both economical and clinical factors play a role. Whereas imipenem is the cheaper carbapenem, ertapenem has the potential advantage that it is only given once daily; and meropenem is by some authors believed to be the most effective in humans, but no head-to-head comparison studies have confirmed this to date. Therefore, more clinical evidence and dose optimization substantiated for example by hollow fiber infection studies are needed to support the repurposing carbapenems for the treatment of M/XDR-TB.

Clinical studies are hampered by the fact that currently no combination of a carbapenem with clavulanate is commercially available. Furthermore, clavulanate is not available alone so at present it is not practically possible to prescribe carbapenem with clavulanate. Therefore, amoxicillin – clavulanate is often co-administered along with a carbapenem in case the latter is preferred for treatment. Unfortunately, amoxicillin has gastrointestinal side effects potentially complicating prolonged treatment. Therefore, combined treatment amoxicillin– clavulanate with a carbapenem is only an option for TB treatment of complicated cases showing multi- or extensive drug resistance \(^{42}\). Although, Gonzalo \textit{et al.} reported a potential benefit that MIC values drop when amoxicillin is added to a combination of meropenem and clavulanate.

Due to different procedures, analytical methods and design, the biochemical instability of the drugs of interest, the short half-live of drugs of interest in mice, diversity in MIC determination and intolerance in addition to resistance, it was not possible to perform a meta-analysis. While the observational data are promising, carbapenems can only recommended in case of resistance to group A and group B drugs in M/XDR-TB treatment.
The ideal carbapenem would have the antimycobacterial activity of imipenem, the half-life of ertapenem and the oral bioavailability of tebipenem-pivoxil. Due to increasing resistance observed in XDR-TB isolates (66-67) and in MDR-TB patients with resistance to an aminoglycoside, carbapenems may be a valuable alternative to the current injectable second line drugs. Assessment of intracellular activity as well as activity against dormant M. tuberculosis by carbapenems is a critical step to further explore the potential of these repurposed drugs.

As successful treatment outcome for M/XDR-TB is still poor, ranging from 25-50% (1) an improvement of the current treatment is urgently needed. An individual data meta-analysis among 12,030 individual patients from 50 studies showed a significantly better treatment outcome for patients who received carbapenems compared to other drugs traditionally used for treatment of MDR-TB. (68). Since there is a need for new or repurposed drugs for the treatment of M/XDR-TB, phase II/III clinical trials are urgently needed for carbapenems to further evaluate their potential. Long term safety and activity against M. tuberculosis are supported by observational data and several studies (41,50,69). A phase II prospective randomized controlled study evaluating a carbapenem plus a BLaC inhibitor on top of an optimized background regimen versus standard of care would be an appropriate strategy to test the potential benefits of carbapenems for M/XDR-TB treatment.

Conclusion

Now the variable results of in vitro studies have been explained and the activity of carbapenems in the presence of a BLaC inhibitor is established, these drugs should be further developed for the treatment of multi- and extensive drug resistant M. tuberculosis. Ultimately, a well-designed phase 2 study is needed to substantiate the claimed benefits of carbapenems in patients with drug-resistant TB.

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Cecile Magis-Escurra, Richard M Anthony, Adri G M van der Zanden, Dick van Soolingen, Jan-Willem C Alffenaar. 2018. Pound foolish and penny wise—when will dosing of rifampicin be optimised? The Lancet Respiratory Medicine
Table 1: Results of the in vitro studies reporting on carbapenems
N: number of strains, MIC: Minimal inhibitory concentration (mg/L), MIC50: Minimal inhibitory concentration required to inhibit growth of 50% of the organisms, MIC90: Minimal inhibitory concentration required to inhibit growth of 90% of the organisms, CLV: clavulanate (mg/L), MBC99: minimal bactericidal concentration that kills 99% of replication culture (mg/L), CFU: colony forming units (Log/(CFU/ml))

Table 2: Results of the in vivo studies reporting on carbapenems
MIC: Minimal inhibitory concentration (mg/L), CLV: clavulanate (mg/L), MBC: minimal bactericidal concentration (mg/L), CFU: colony forming units. qd: once a day, bid: twice a day, tid: three times a day, qid: four times a day

Table 3: Results of the in human studies reporting on carbapenems
qd: once a day, bid: twice a day, tid: three times a day, qid: four times a day. PK: pharmacokinetic, ND: not described
Pubmed: 250 articles
Web of Science: 260 articles

510 articles

Removal of 146 duplicates

364 articles remained for screening

Removal of 320 articles after screening title and abstract

46 articles remaining for screening full text evaluation

Removal of 12 articles: reasons for exclusion:
- Not available (n=6),
- Other drug (n=2),
- No MIC (n=1),
- Case-report (n=1),
- Other (n=2)

34 Relevant articles were included in this study
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<th>First author and reference</th>
<th>Strain</th>
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<td>Deshpande et al (47)</td>
<td>H37Ra, HEP 1 monocytes</td>
<td>1</td>
<td>Resazurin microdilution assay, CFU counts</td>
<td>Faropenem</td>
<td>None</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dhar et al (49)</td>
<td>H37Ra, Erdman</td>
<td>2</td>
<td>96 Well flat-bottom polystyrene microtiter plate</td>
<td>Faropenem</td>
<td>Meropenem</td>
<td>1.3</td>
<td>2.5</td>
<td>2.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.71 log</td>
</tr>
<tr>
<td>England et al (40)</td>
<td>H37Ra, macrophages</td>
<td>1</td>
<td>CFU counts</td>
<td>Meropenem</td>
<td>Clavulanate</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 log</td>
</tr>
<tr>
<td>Forsman et al (41)</td>
<td>H37Ra, Clinical isolates</td>
<td>69</td>
<td>Broth microdilution</td>
<td>Meropenem</td>
<td>Clavulanate</td>
<td>0.125-12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gonzalo et al (42)</td>
<td>H37Ra, Clinical isolates</td>
<td>28</td>
<td>96 MGIT system</td>
<td>Meropenem</td>
<td>Clavulanate</td>
<td>resistant at 5 mg/L</td>
<td>(1.28 - 2.56)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gurumurthy et al (48)</td>
<td>H37Ra</td>
<td>1</td>
<td>96 Wells plate</td>
<td>Faropenem</td>
<td>None</td>
<td>5-10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0 log</td>
</tr>
<tr>
<td>Horita et al [43]</td>
<td>H37Rv, Clinical isolates</td>
<td>42</td>
<td>Broth microdilution</td>
<td>Meropenem</td>
<td>Biapenem</td>
<td>Teipenem</td>
<td>Clavulanate (Avibactam)</td>
<td>1:32</td>
<td>1:32</td>
<td>0.25-8</td>
<td>16</td>
<td>16</td>
<td>32</td>
</tr>
</tbody>
</table>

Table 1: Results of the in vitro studies reporting on carbapenems
<table>
<thead>
<tr>
<th>Study</th>
<th>Strain or Cells</th>
<th>Methods</th>
<th>Bacteria Tested</th>
<th>MIC Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hugonnet et al (8)</td>
<td>Erdman, H37Rv, Clinical isolates</td>
<td>Broth microdilution</td>
<td>Imipenem, Meropenem, Clavulanate</td>
<td>0.16-0.25</td>
</tr>
<tr>
<td>Kaushik et al (33)</td>
<td>H37Rv, Clinical isolates</td>
<td>Broth microdilution</td>
<td>Imipenem, Meropenem, Ertapenem, Doripenem, Biapenem, Faropenem, Telipenem, Panipenem</td>
<td>0.16-1.25</td>
</tr>
<tr>
<td>Kaushik et al (51)</td>
<td>H37Rv, strain 115R, strain 124R</td>
<td>Broth microdilution</td>
<td>Biapenem, None</td>
<td>&gt;80</td>
</tr>
<tr>
<td>Sala et al (44)</td>
<td>18b cells</td>
<td>Serial dilutions, CFU counts</td>
<td>Meropenem, Clavulanate</td>
<td>None</td>
</tr>
<tr>
<td>Solapure et al (34)</td>
<td>H37Rv, 18b cells</td>
<td>Resazurin microdilution assay, CFU counts</td>
<td>Imipenem, Meropenem, Faropenem</td>
<td>0.5-2</td>
</tr>
<tr>
<td>Srivastava et al (45)</td>
<td>H37Ra</td>
<td>Resazurin microdilution assay</td>
<td>Ertapenem, Clavulanate</td>
<td>2.38 log10</td>
</tr>
<tr>
<td>Yaziri et al (35)</td>
<td>H37Rv</td>
<td>Broth microdilution</td>
<td>Imipenem, Meropenem, Ertapenem</td>
<td>16-4</td>
</tr>
</tbody>
</table>
Table 2: Results of the in vivo studies reporting on carbapenems

<table>
<thead>
<tr>
<th>First author (ref.)</th>
<th>Strain</th>
<th>Mice</th>
<th>Infection model</th>
<th>Drug</th>
<th>Dose</th>
<th>Treatment</th>
<th>End-point</th>
<th>Organs</th>
<th>CFU reduction</th>
<th>Survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chambers et al (52)</td>
<td>H37Rv</td>
<td>CD-1 Female mice</td>
<td>subcutaneously</td>
<td>Imipenem</td>
<td>Bid 100 mg/kg</td>
<td>CFU count, Survival rate</td>
<td>Spleen, lungs</td>
<td>1.8 log</td>
<td>65%</td>
<td>ND</td>
</tr>
<tr>
<td>Dhar et al (49)</td>
<td>H37Rv</td>
<td>adult C57BL/6J mice</td>
<td>intratracheal</td>
<td>Faropenem</td>
<td>500 mg/kg</td>
<td>CFU count</td>
<td>Lungs</td>
<td>reduction of CFU: 10^5 - 10^6</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>England et al (40)</td>
<td>H37Rv</td>
<td>C57BL/6 Mice</td>
<td>subcutaneously</td>
<td>Meropenem</td>
<td>bid 300 mg/kg</td>
<td>Chronic stage</td>
<td>CFU count</td>
<td>1 log</td>
<td>ND</td>
<td>1 log</td>
</tr>
<tr>
<td></td>
<td></td>
<td>New Zealand white rabbits</td>
<td>intravenous bolus</td>
<td>Meropenem</td>
<td>75 mg/kg, 125 mg/kg</td>
<td>PK data</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Kaushik et al (51)</td>
<td>H37Rv</td>
<td>BALB/c mice</td>
<td>Aerosol</td>
<td>Biapenem</td>
<td>200 mg/kg BID, 300 mg/kg BID</td>
<td>Late phase acute TB, rifampicin-resistant TB</td>
<td>CFU count</td>
<td>Lungs</td>
<td>1 log</td>
<td>ND</td>
</tr>
<tr>
<td>Rullas et al (53)</td>
<td>H37Rv</td>
<td>TF3157 DHP-I KO mice</td>
<td>subcutaneously</td>
<td>Meropenem, Faropenem</td>
<td>TID 300 mg/kg, TID 500 mg/kg</td>
<td>Acute TB model</td>
<td>CFU count</td>
<td>Lungs</td>
<td>1.7 log, 2 log</td>
<td>ND, ND</td>
</tr>
<tr>
<td>Solapure et al (34)</td>
<td>H37Rv</td>
<td>BALB/c mice</td>
<td>Aerosol</td>
<td>Meropenem</td>
<td>TID 300 mg/kg</td>
<td>Acute and chronic model</td>
<td>CFU count</td>
<td>Lungs</td>
<td>no reduction</td>
<td>no reduction</td>
</tr>
<tr>
<td>Veziris et al (35)</td>
<td>H37Rv</td>
<td>Female Swiss mice</td>
<td>Intravenously</td>
<td>Imipenem, Meropenem, Ertapenem</td>
<td>100 mg/kg</td>
<td>Preventive model</td>
<td>CFU count, Survival rate</td>
<td>Spleen, lungs</td>
<td>&gt;1.2 log*, &gt;1.8 log*, &gt;1.7 log*</td>
<td>1 dead, 3 dead, 3 dead</td>
</tr>
</tbody>
</table>

*ND indicates not determined.
<table>
<thead>
<tr>
<th>First author (ref)</th>
<th>Year of publication</th>
<th>Country</th>
<th>Study population</th>
<th>Study design</th>
<th>Drug</th>
<th>Dosage</th>
<th>Patients</th>
<th>Paediatric</th>
<th>Sputum Smear</th>
<th>Sputum culture</th>
<th>Treatment success</th>
<th>Adverse events</th>
<th>Interruption due AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arbet et al (54)</td>
<td>2016</td>
<td>Brazil</td>
<td>2013 - 2015</td>
<td>Observational, retrospective</td>
<td>Imipenem</td>
<td>1 g oc</td>
<td>12</td>
<td>No</td>
<td>12/12</td>
<td>12/12</td>
<td>7/12</td>
<td>0/12</td>
<td>0/12</td>
</tr>
<tr>
<td>Chambers et al (52)</td>
<td>2005</td>
<td>USA</td>
<td>ND</td>
<td>Prospective</td>
<td>Imipenem</td>
<td>1 g bid</td>
<td>10</td>
<td>No</td>
<td>ND</td>
<td>8/10</td>
<td>7/10</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>De Lorenzo et al (58)</td>
<td>2014</td>
<td>Italy, The Netherlands</td>
<td>2001-2012</td>
<td>Observational case-control</td>
<td>Meropenem</td>
<td>1 g tid</td>
<td>37</td>
<td>No</td>
<td>28/32</td>
<td>31/37</td>
<td>ND</td>
<td>5/37</td>
<td>2/5</td>
</tr>
<tr>
<td>Payen et al (57)</td>
<td>2018</td>
<td>Belgium</td>
<td>2009-2016</td>
<td>Retrospective case series</td>
<td>Meropenem</td>
<td>2 g bid (then bid)</td>
<td>18</td>
<td>No</td>
<td>16/18</td>
<td>16/18</td>
<td>15/18</td>
<td>0/18</td>
<td>0/18</td>
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<tr>
<td>Palmero et al (59)</td>
<td>2015</td>
<td>Argentina</td>
<td>2012-2013</td>
<td>Retrospective</td>
<td>Meropenem</td>
<td>2 g tid (then 1 g tid)</td>
<td>10</td>
<td>No</td>
<td>ND</td>
<td>8/10</td>
<td>3/6</td>
<td>0/10</td>
<td>ND</td>
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<tr>
<td>Van Rijn et al (10)</td>
<td>2016</td>
<td>The Netherlands</td>
<td>2010-2013</td>
<td>Retrospective</td>
<td>Ertapenem</td>
<td>1 g oc</td>
<td>18</td>
<td>yes</td>
<td>ND</td>
<td>15/18</td>
<td>15/18</td>
<td>2/18</td>
<td>3/18</td>
</tr>
<tr>
<td>Tiberi et al (61)</td>
<td>2016</td>
<td>Italy, The Netherlands</td>
<td>2008-2015</td>
<td>Retrospective, cohort</td>
<td>Ertapenem</td>
<td>1 g oc</td>
<td>5</td>
<td>No</td>
<td>3/5</td>
<td>3/5</td>
<td>4/5</td>
<td>0/5</td>
<td>0/5</td>
</tr>
<tr>
<td>Tiberi et al (60)</td>
<td>2016</td>
<td>Italy, The Netherlands</td>
<td>2003-2015</td>
<td>Observational, retrospective, cohort</td>
<td>Meropenem</td>
<td>1 g tid (2g tid)</td>
<td>96</td>
<td>No</td>
<td>55/58</td>
<td>55/58</td>
<td>55/96</td>
<td>6/93</td>
<td>8/94</td>
</tr>
</tbody>
</table>
Tiberi et al (11, 55) 2016 - 2003-
2015
Observational retrospective

case-control

Imipenem 500 mg qid

84

No

51/64 51/64 34/57 3/56 4/55