Anti-microbial resistance: Choice of treatment of infections caused by multidrug-resistance Gram-negative pathogens

DRAFT REPORT

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PREFACE

This report was prepared for European Medical Agency (EMA) according to framework contract EMA/2015/24/PH. The work described in this report was carried out by the Department of Clinical Epidemiology (DCE), Aarhus University Hospital, Aarhus, Denmark.

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Introduction

Use of antibiotics, not only overuse and misuse, in both humans and animals has been a main factor accelerating the process of antibiotic or antimicrobial resistance worldwide (1). Antimicrobial resistance is the ability of disease-causing bacteria (i.e. pathogens) to change and resist the effects of several drugs, created to destroy pathogens or to stop them from growing and multiplying (2). Several biochemical mechanisms of resistance exist, including mutational alteration of the target protein, enzymatic inactivation of the antibiotic drug, acquisition of genes for less susceptible target proteins from other species, bypassing of the target or preventing drug access to the target (3). All types of bacteria have the ability to become drug-resistant, and occurrence of resistance has been observed for almost all antibiotics that have been in common use (4). During the last decades, several bacterial pathogens have evolved into multidrug-resistant (MDR) forms both in developed and developing countries at an expanding rate (5, 6)(7).

Some of the most important MDR pathogens that currently cause infection in hospital and in the community are the so-called "ESKAPE" pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa, and Enterobacter species*), emphasizing their capacity to "escape" the effects of routine antibiotics (8, 9). Of special concern are several MDR Gram-negative pathogens such as *enterobacteriaceae* (mostly *Klebsiella (K) pneumoniae* and extended-spectrum beta-lactamase [ESBL] producing *enterobacteriaceae*), *Pseudomonas (P) aeruginosa*, and *Acinetobacter (A)* species (10), which are becoming resistant to almost all antibiotics available, creating situations reminiscent of the pre-antibiotic era (11). *K. pneumoniae* can cause nosocomial pneumonia, bloodstream infections, wound or surgical site infections, meningitis as well as urinary tract infection, and has developed extensive antimicrobial resistance, most recently to carbapenems (12). According to the European Centre for Disease Prevention and Control Antimicrobial Resistance Surveillance Network (EARS-Net) (13), 22% of all K. pneumoniae were resistant in 2011 to at least three antimicrobial classes, and a substantial increase in resistance to carbapenems in K. pneumoniae from 8% to 15% was reported over the period 2005–2010. ESBL-producing enterobacteriaceae are responsible for a variety of community-onset and hospital-acquired infections and are associated with poor clinical outcomes (14, 15). *P. aeruginosa* is one of the main causes of serious nosocomial infections in Europe including pneumonia, bloodstream infections, and urinary tract infections (16). Antimicrobial resistance in *P. aeruginosa* is common in Europe, with a majority of the 29 EARS-Net countries reporting resistance above 10 % for

all antimicrobial groups under surveillance (13). In addition, 15% of *P. aeruginosa* infections were resistant to at least three antimicrobial groups and 6% were resistant to all five antimicrobial groups under regular EARS-Net surveillance (13). Centers for Disease Control and Prevention has estimated that 6,700 cases of MDR *P.* aeruginosa occur annually in United States causing 440 deaths (4). *A. baumannii* can cause a variety of infections including pneumonia and bloodstream infections, which are associated with high mortality and morbidity (17, 18). Today, *A. baumannii* has extensive resistance to most first-line antibiotics (19). Centers for Disease Control and Prevention has estimated that 7,300 of MDR *A. baumannii* infections occur annually in United States, causing 500 deaths (4). *A. baumannii* has also become an issue in war conflict zones and has spread particularly in the United Kingdom and the United States (20).

Other MDR Gram-negative bacteria are emerging, e.g. *Stenotrophomonas (S) maltophilia*. Infections due to *S. maltophilia* have a high mortality and incidence of hospital-acquired infection due to *S. maltophilia* is increasing, particularly in the immunocompromised patient population. Further, cases of community-acquired *S. maltophilia* have also been reported (21).

The World Health Organization has recently identified antimicrobial resistance as one of the three most important problems facing human health (6). MDR infections constitute a serious public health problem because they are difficult to treat effectively, leading to longer hospital stays, treatment failures, and adverse outcomes such as complications and death (1, 22). The prevalence of MDR Gram-negative bacteria varies considerable across the world. For example, quinolone resistance in urinary E.coli has been reported to be as high as 70% in China and India, whreas 4.2% of E.coli were resistant to third-generation of cephalosporins and 6.9% were resistant to fluoroquinolones. In addition, carbapenem resistance is 60% in K. pneumoniae in Greece, whereas is is reported to be 0.2% in the Netherlands (23) Analyses from the European Centre for Disease Prevention and Control in 2009 estimated that infections caused by a subset of resistant bacteria are responsible for about 25,000 deaths in Europe annually (24). The overall crude economic burden of antibiotic resistance in Europe has been estimated to at least 900 million Euro in healthcare costs and 600 million Euro a year in lost productivity (22, 25).

Despite the rise in MDR organisms, there is a scarcity of data on which antimicrobial treatment, alone or in combination, is currently guideline-recommended in Europe and used in clinical practice. Available guidelines that are used in Europe come from the US and Australia (26). For example, the University of Washington offers specific detailed recommendations for anti-

biotic dosage and treatment of e.g. MDR *Pseudomonas* and *Acinetobacter*. In Australia, specific antibiotic treatment recommendations for MDR bacteria in urology (27) and for third-generation cephalosporin-resistant *enterobacteriaceae* and carbapenem-resistant *enterobacteriaceae* (28) are in place. These guidelines are not fully applicable to European countries due to the difference in incidence of Gram-negative bacteria and healthcare systems. Also, the most recent data used in these guidelines are from 2015, which, because of the expanding evolution of MDR gram negative bacteria, may already be obsolete. Current European guidelines, available in English, mostly focus on preventative measures thought to reduce the occurrence of MDR Gram-negative bacteria, including hygienic measures, strict MDR control, and antimicrobial stewardship. But controversies regarding even prevention are found throughout Europe (29).

In conclusion, current official recommendations in Europe are based on systematic reviews that suggest different methods to prevent and control MDR Gram-negative infections, but provide little data on new and alternative antibiotic treatment options and therefore provide little firm guidance on specific treatment choices and algorithms (8, 30-35). Previous systematic reviews are based on studies that are heterogeneous and are struggling with small, diverse populations from single centers, comparing various antimicrobial treatment options and providing different results. Clinical data addressing these considerations are neither overwhelming nor definitive (36, 37).

Objectives

To investigate, systematically, the available literature and guidelines, as well as to capture the current practice for treatment of infections due to MDR Gram-negative pathogens for which limited therapeutic options are available.

Specific objectives:

1. To perform systematic review of all relevant published articles and reports providing guidelines on treatment options for MDR Gram-negative infections (Study 1).
2. To investigate, using a cross-sectional survey of pharmacists or clinicians in a range of selected reference hospitals, current treatment protocols and/or antibiotics prescribing patterns used to treat infections due to MDR Gram-negative pathogens, irrespective of the body site (Study 2).
3. To perform cohort study with patient-level information within hospitals on pattern of prescriptions (e.g. frequency, duration, switching) and relevant outcome data (Study 3).

Study 1 - Systematic literature review

1. Aim

The purpose of this systematic review was to identify and critically appraise current evidence-based antimicrobial treatment options for infections with MDR Gram-negative bacteria, focusing on infections with *P. aeruginosa*, *A. baumannii*, ESBL-producing *enterobacteriaceae* and *S. maltophilia* in an attempt to provide guidance for specific treatment choices and algorithms.

2. Methods

2.1. Eligibility criteria

We included randomized studies (clinical trials, controlled clinical trials, randomized controlled trials), observational studies, meta-analyses, reviews, systematic reviews, and guidelines that investigated any antimicrobial treatment for infections caused by MDR Gram-negative bacteria (*P. aeruginosa*, *A. baumannii*, ESBL-producing *enterobacteriaceae*, or *S. maltophilia*).

Our population of interest was adult patients, 18 years or older, who had a confirmed MDR infection and received antimicrobial treatment. We included studies that evaluated the outcomes of specific MDR Gram-negative bacteria with regard to the administered antimicrobial treatment. Studies directly comparing outcomes following different antibiotic treatments were of particular interest. However, we also included studies reporting on outcome of specific treatments without a comparison treatment group. Our primary outcome of interest included clinical success from initiation of treatment until discharge or death. Clinical success was defined as complete resolution or substantial improvement of signs and symptoms of the index infection, such that no further antibacterial therapy was necessary. Our secondary outcomes were mortality irrespective of follow-up time after infection or initiation of treatment and microbiological success measured by microbiological response, suppression or eradication, bacteriological count, and laboratory outcome.

Studies published from 2006-2017 in English were included. In addition, studies under publication or unpublished studies conducted at Aarhus University by the co-authors (medical students SMN, CSJ and JA) were included (38).

2.2. Information source

Studies were identified by searching electronic databases (MEDLINE through PubMed) for articles and scanning reference lists of the included published articles. We limited our search to English to reflect the language capabilities of our team. Our search started on 20 September 2017 and ended on 29 September 2017.

2.3. Literature search

Our search strategy included the following search terms ”multidrug resistant” AND “gram negative bacteria” AND ”Escherichia coli” OR ”Pseudomonas aeruginosa” OR ”Acinetobacter baumannii” OR ”Stenotrophomonas maltophilia” OR ”ESBL”. The search terms covered title of the papers.

We limited our search to the English language and to studies published from 1 January 2006 to 1 September 2017; and studies on adult patients (≥18 years). MeSH terms were not used to ensure that the latest published articles were part of the search result.

2.4. Study selection

Our initial search targeted articles that 1) evaluated infections with MDR *E. coli, P. aeruginosa, A. baumannii, S. maltophilia,* or ESBL *enterobacteriaceae*, 2) mentioned a potential antimicrobial treatment, and 3) included information on outcome of treatment. We included studies with any method of diagnosing MDR infection and any antimicrobial treatment. Any site of infection was included as well, e.g. respiratory tract and blood stream.

Studies were selected through a three-stage selection process:

First, a literature search for articles on the MDR Gram-negative bacteria included in the title was performed independently by three co-authors (SMN, CSJ and JA) with selection of relevant papers.

At the second stage, abstracts were reviewed against two other eligibility criteria (administered antimicrobial treatment and outcome of interest) by three co-authors (SMN, CSJ and JA). Due to different nomenclature for MDR, we decided, after consulting with a senior author (ABP), to include different synonyms (e.g. carbapenem-resistance and XDR) in the study selection process to insure inclusion of all articles concerning MDR bacteria. The latest search was done on 27 September 2017.

At the third stage, the included articles were distributed evenly between the three co-authors (SMN, CSJ and JA) and examined in detail according to a predefined extraction form.

At each stage, disagreements about fulfilment of eligibility criteria between co-authors (SMN, CSJ and JA) were resolved by consensus or in consultation with a senior author (ABP).
Due to lack of material, consensus between the three co-authors (SMN, CSJ and JA) was made to overlook the age criteria when including articles regarding *S. maltophilia*.
The results of our search strategy and selection process are presented in Figure 1.

2.5. Data extraction and assessment of quality of the studies

We developed a structured data extraction form, pilot-tested it on six included studies and refined it accordingly.
The following information on all included studies was extracted: author names, year of publication and country of origin, study design, study period, characteristics of the study population (size, age, inclusion criteria, and site of infection), follow-up time, antimicrobial treatment and administration, outcome evaluated, factors reported as being adjusted for, statistical analyses, and risk estimates with p-values. Each review author presented extracted data and discussed with the other two review authors. If a review author had any doubt regarding extracted data, the paper was reviewed by another review author and disagreements were resolved by discussion between the two review authors or in consultation with a senior author.
Duplicate publications were removed continuously.
Quality and risk of bias in individual studies were assessed at the study and outcome level by three authors jointly (SMN, CSJ and JA), using the Study Quality Assessment Tool from The National Heart, Lung and Blood Institute (39). The results of the quality assessment are presented in Table 1-4. Each study was quality rated according to one of the following categories: poor quality 0-40%, fair quality 41-80%, and good quality 81-100% based on the proportion of yes answers among all relevant questions (39). Disagreements about quality assessment between three co-authors were resolved by consensus or in consultation with a senior author.

2.6. Summary measures

The following measures of treatment were included: absolute risks, absolute risk difference, p-values, hazard ratio (HR), relative risk, and odds ratio with 95% confidence intervals (CI). Unadjusted and adjusted measures were included if available.

2.7. Planned methods of analyses

We focused primarily on describing the studies, their results, their applicability, and their limitations and on a qualitative synthesis of the results.

We have further planned to quantifying effect measures in a weighted formal meta-analysis if there is a consistency in the study designs, participants, antimicrobial treatment, and reported outcome measures.

3. Results

3.1. Study selection

The literature search yielded 580 studies.

After initial screening of titles for eligibility criteria, 380 studies were excluded.

After screening of the remaining 200 abstracts, 133 articles were further excluded because they did not meet the eligibility criteria.

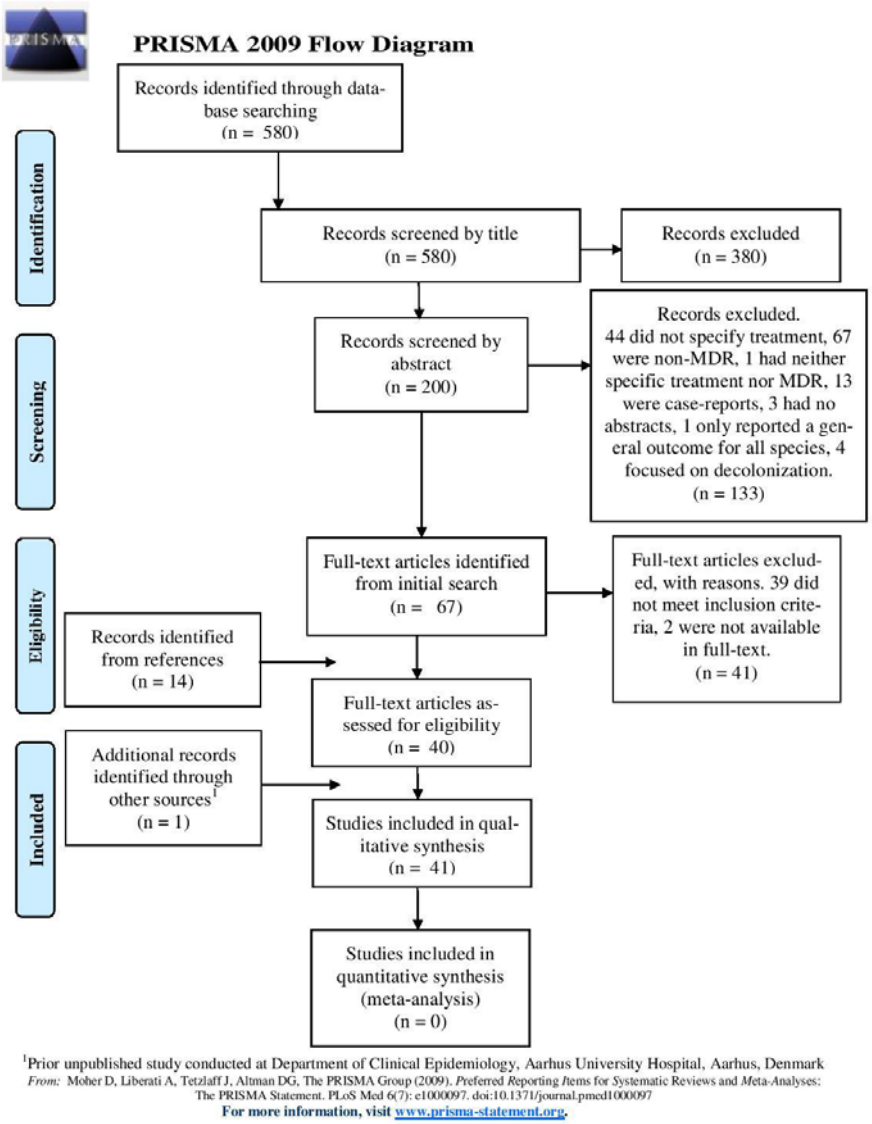
After reviewing the 67 full-text articles, 41 articles were excluded because they did not fulfill the eligibility criteria.

An additional 14 articles were identified and included by checking the references of located, relevant papers and 1 additional article was included from a prior unpublished study conducted at Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark by the co-authors SMN, CSJ and JA.

A total of 41 articles were included in the qualitative systematic review (Figure 1).

Characteristics and quality of the included studies are presented in Tables 1-4. The heterogeneity of the included articles prevents us from doing a meta-analysis.

Figure 1: PRISMA Flow Diagram



3.2. P. aeruginosa

3.2.1. Results regarding choice of treatment and outcomes for P. aeruginosa

Four studies were included, two observational studies (40, 41), and two randomized controlled studies (42, 43). Results are presented in Table 1.

Sorli et al. investigated the effect of intravenous colistimethate sodium among 91 patients infected with *P. aeruginosa* at any site, except acute bronchitis and tracheitis. No comparison group with antibiotic treatment or placebo was applied. Clinical success occurred in 72 patients (79%) after 30 days of follow-up. The 30-day all-cause mortality was 30.8%. The mean plasma level of colistin steady state (Css) level was 1.49 mg/L in patients with clinical success and 2.42 mg/L (p=0.01) in patients with clinical failure, however, Css was not observed to be related to either clinical success or mortality (40).

Wright et al. evaluated treatment with bacteriophage preparation (biophage-PA) compared with placebo in 24 patients with chronic otitis caused by antibiotic resistant P. *aeruginosa*. Clinical success was determined in the way tha physician assessed erythema/inflammation, ulceration/granulation/polyps, discharge quantity, discharge type and odour using a Visual Analogue Scale (VAS). Mean VAS reduction was 50% in treatment group and 20% in placebo group compared with baseline. The treated group had the statistically significant reduction in median P. aeruginosa counts on day 21 (p=0.01) and day 42 (p=0.02) compared with baseline. The placebo group had a reduction in median pseudomonas counts at day 7, 21 and 42, but the reduction was not significant (42). Pooled patient- and physician-reported clinical indicators of success improved for treated relative to placebo group.

Montero et al. retrospectively evaluated treatment with colistin monotherapy and colistin combination therapy (aminoglycosides, b-lactams, quinolones, and carbapenems) in 121 patients infected with MDR *P. aeruginosa* at different infection sites. The proportion of patients with clinical success was similar in the colistin monotherapy-group (73%) compared to colistin combined ociated with four other antibiotics (72%, 72%, 75%, and 66%, respectively). A favorable outcome was found in all sites of infection; bronchial infection (73%), bacteremia (63%), pneumonia (65%), urinary tract infection (85%), and soft tissue infections (73%) (41).

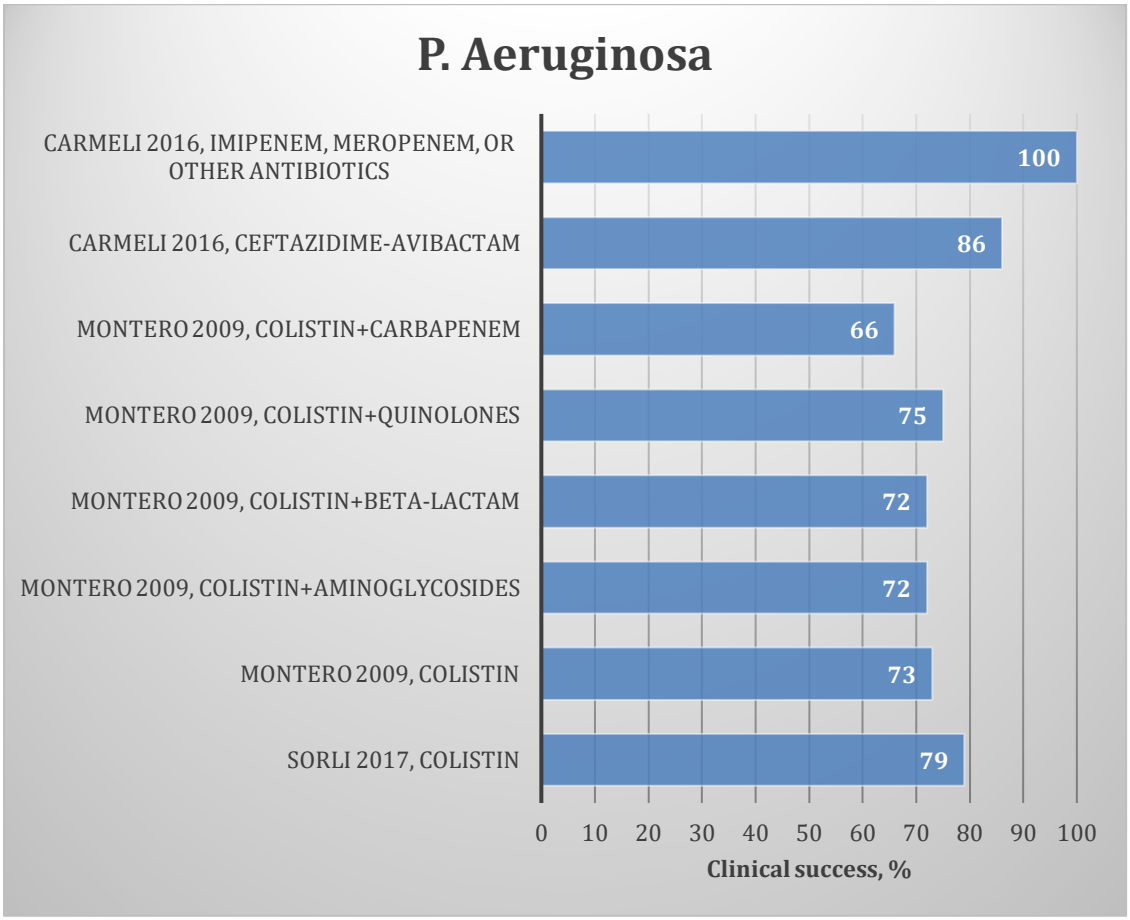
Carmeli et al. investigated ceftazidime-avibactam compared to best available treatment (including imipenem (53%), meropenem (34%), and other antibiotics (13%)) for patients with urinary tract infection or complicated intra-abdominal infection (cIAI) caused by MDR *P. aeruginosa* or ESBL-producing *enterobacteriaceae*. 19 patients had urinary tract infection and 20 had cIAI due to MDR *P. aeruginosa*. Clinical and microbiological success in patients with

P. aeruginosa specific urinary tract infection occurred in 86% / 79% of patients treated with ceftazidime-avibactam and 100% / 60% of patients treated with best available treatment. All patients with cIAI had clinical and microbiological success independent of treatment (43).
Clinical success for different treatment options is presented in Figure 2.

3.2.2. Conclusion for P. aeruginosa

Four studies were included reporting treatment effect for MDR *P. aeruginosa*. Studies were characterized by heterogeneity of study design, site of infection, and treatment used. Clinical success was evaluated in all four studies, in addition to 30-day mortality or microbiological success. Largest study population included 121 patients.
Patient and physician-reported clinical indicators improved in the Biophage-PA-treated group compared with the placebo group. Studies based on larger sample size, studies that directly compare Biophage-PA treatment to antibiotic treatment, as well as studies including other infection sites would be enlightening.
Clinical success between 70% and 100% was reported in three other studies irrespective of the type of antibiotic treatment. High clinical success rate up to 100% was seen in randomized study of Carmeli et al. where a number of exclusion criteria was applied; f.eks. both patients with complicated urinary tract infection and intra-abdominal infection were excluded, as as patients with evidence of abnormal liver function, and patients that were unlikely to respond to ceftazidime-avibactam treatment. Due to small sample sizes and variability in the type of antibiotics used, it is not possible to recommend one specific antibiotic over another.

Figure 2. Results regarding choice of treatment and clinical success for *P. aeruginosa*



3.3. A. baumannii

3.3.1. Results regarding choice of treatment and outcomes for *A. baumannii*

We identified 19 studies, of which 14 were observational studies (44-57), and five were randomized controlled studies (58-62). Study characteristics and quality assessment are shown in Table 2. Studies were based on populations with different site of infections (airways, bloodstream, abdomen, skin, and meninges) and study population size varied from 10 to 250 patients.

Four articles (two randomized and two retrospective observational studies) compared colistin monotherapy to colistin combination therapy. Yilmaz et al. reported among patients with ventilator associated pneumonia a clinical success of 77% for colistin monotherapy compared to 64% and 55% for colistin-carbapenem therapy and colistin-sulbactam therapy, respectively (p=0.35) (46). Sirijatupha et al. reported a clinical success of 63% for colistin monotherapy and 56% for colistin-fosfomycin combination therapy (p=0.65) (58). Batirel et al. showed a clinical

success rate of 31% for monotherapy and 46% for colistin combination therapy (carbapenem, sulbactam, and other agents) (p=0.19) (48). Finally, Aydemit et al reported that clinical success in patients treated with colistin monotherapy was 52% compared to 41% in patients treated with colistin-rifampicin (p=0.65) (59). Results are presented in Table 2.

There were controversies regarding microbiological success for colistin compared with combination therapy with carbapenem or sulbactam. Based on 70 patients with ventilator-associated pneumonia infection, Yilmaz et al. found no significant difference in microbiological success (colistin 51%, colistin-carbapenem 64%, and colistin-sulbactam 60% p=0.23) (46), while Batirel et al. found that their 250 patients treated with combination therapy for bloodstream infection had a better microbiological outcome (colistin 80%, colistin combination therapy 57% p=0.001) (48). It should be mentioned that Batirel et al. also included combination therapy with other antibiotics than sulbactam and carbapenem, such as tigecycline, amikacin, netilmicin, gentamicin, aminoglycoside, rifampicin, and piperacillin-tazobactam (48). Durante-Mangoni et al. and Aydemir et al. both compared colistin monotherapy to colistin-rifampicin combination therapy in 210 patients with life-threatening infections due to MDR *A. baumannii* from intensive care units and 43 patients with ventilator-associated pneumonia caused by carbapenem resistant *A. baumannii* strain, respectively. Durante-Mangoni et al. found that microbiological success was significantly higher for combination therapy (45% vs. 61% p=0.03) (62), whereas Aydemir et al. found no significant difference in microbiological success between colistin combination and monotherapy (71% vs. 59% p=0.59) (59).

Two studies examine the outcome of therapy with ampicillin-sulbactram compared with colistin eller comparing to another dosis of ampicillin-sulbactram. Therapy with ampicillin-sulbactam was not superior to colistin monotherapy regarding clinical success (62% vs. 60% p=not significant [NS]), 14-day mortality (15% vs. 20% p=NS), 28-day all-cause mortality (30% vs. 33% p=NS) among 28 patients with MDR *A. baumannii* ventilator-associated pneumonia (60). Betrosian et al. (61) compared two different doses of ampicillin-sulbactam, 18/9 g/day (low dose) vs. 21/12 g/day (high dose) among 27 patients with ventilator-associated pneumonia infection and found that clinical success rates were 64% in the low dose group and 69% in the high dose group (p=0.785), while microbiological success rates were 86% and 69% (p=0.303), respectively. Both 14-day (21% vs. 31% p=0.580) and 30-day (43% vs. 54% p=0.568) mortality did not differ significantly between the low dose group and the high dose group, respectively (61).

In a study based on 94 patients sustaining MDR *A. baumannii* infection in various sites, comparison of colistin monotherapy vs. colistin-fosfomycin combination therapy showed a favorable microbiological success for patients treated with the combination therapy (100% vs. 85% p=0.02). However, no difference was seen in 28-day all-cause mortality (54% vs. 44% p=0.51) (58).

Tigecycline-based therapy was not superior to colistin-based therapy in terms of microbiological (23% vs. 30%) or clinical success (47% vs. 48%) among 70 patients with MDR *A. baumannii* pneumonia in critically ill patients. In addition, there was no significant difference between the groups in 30-day mortality (33% vs. 30%) (52).

Cheng et al. (54) compared combination therapy with colistin-tigecycline and colistin-carbapenem in relation to mortality. 14-day all-cause mortality was 35% vs. 15% (p=0.12; crude HR=2.6 p=0.09) and all-cause in-hospital mortality was 69% vs. 50% (p=0.15).

Several studies reported outcome of treatment of MDR *A. baumannii* without a treatment comparison group. The study population included various infection sites.

Kwon et al. reported 33% mortality within 30 days of initiation of treatment with colistin monotherapy in patients infected with carbapenem resistant *A. baumannii* (55). Alvarez et al. reported 14% mortality within 30 days after colistin treatment without a loading dose (44). Michalopoulos et al. reported that 83% of patients had a microbiological and clinical success and 25% of patients died during hospital stay after being treated with nebulized colistin against *A. baumannii* ventilator-associated pneumonia (56). Mutauoakkil et al had 100% clinical success after treatment with colistin+rifamipicin among 26 patients admittet to intensive care unit and treated for 15 to 21 days (57).

Several studies evaluated success of treatment with other antibiotics than colistin including: minocycline, tigecycline, and rifampicin/imipenem. Goff et al. investigated the use of minocycline monotherapy compared to minocycline combination therapy and found that minocycline monotherapy showed a tendency to better clinical and microbiological success (100% vs. 71% and 100% vs. 77%, respectively) (53). However, it should be mentioned that only three patients were treated with minocycline monotherapy compared to 52 treated with minocycline combination therapy.

Vasilev et al. found that patients treated with tigecycline had clinical success in 72% of cases and microbiological success in 67% of the cases (49). Ye et al. found that 60% of patients had effect from treatment with tigecycline while 36% died within the first 30 days (51). These two

studies are based on populations of 112 with pneumonia in Ye et al. and 115 patients with bloodstream, skin, abdominal, or airway infection in Vasilev et al.

Bremmer et al. (45) based choice of antibiotic treatment on in vitro checkerboard assays. In group 1, treatment was based on growth inhibition of MDR *A. baumannii* in any well containing serum-achievable concentration of drugs (SAC well). In group 2, treatment was based on growth in all SAC wells. The colistin-tigecycline combination was most frequently used (in 9 of 18 patients), other treatment options included doripenem-colistin (in 5 of 18 patients), minocycline-colistin (in 2 of 18 patients), and doripenem-colistin-tigecycline (in 1 of 18 patients). No significant difference was seen in regards of clinical success (50% vs. 30%, p=0.63) or 30-day all-cause mortality (38% vs. 60%, p=0.63), but a significant effect in microbiological success (88% vs. 30%, p=0.02) between group 1 and 2 was found, favoring treatment based on in vitro inhibition of growth.

Rifampicin/imipenem had a crude mortality rate of 30% and the clinical success rate was 70%. Furthermore, in vitro development of high resistance to rifampicin was shown in 7/10 (70%) of cases based on 10 patients with infection at any site (50). Treatment with rifampicin in combination with colistin showed clinical success in all cases studied based on 26 patients with airway, bloodstream, or meningeal infection (57).

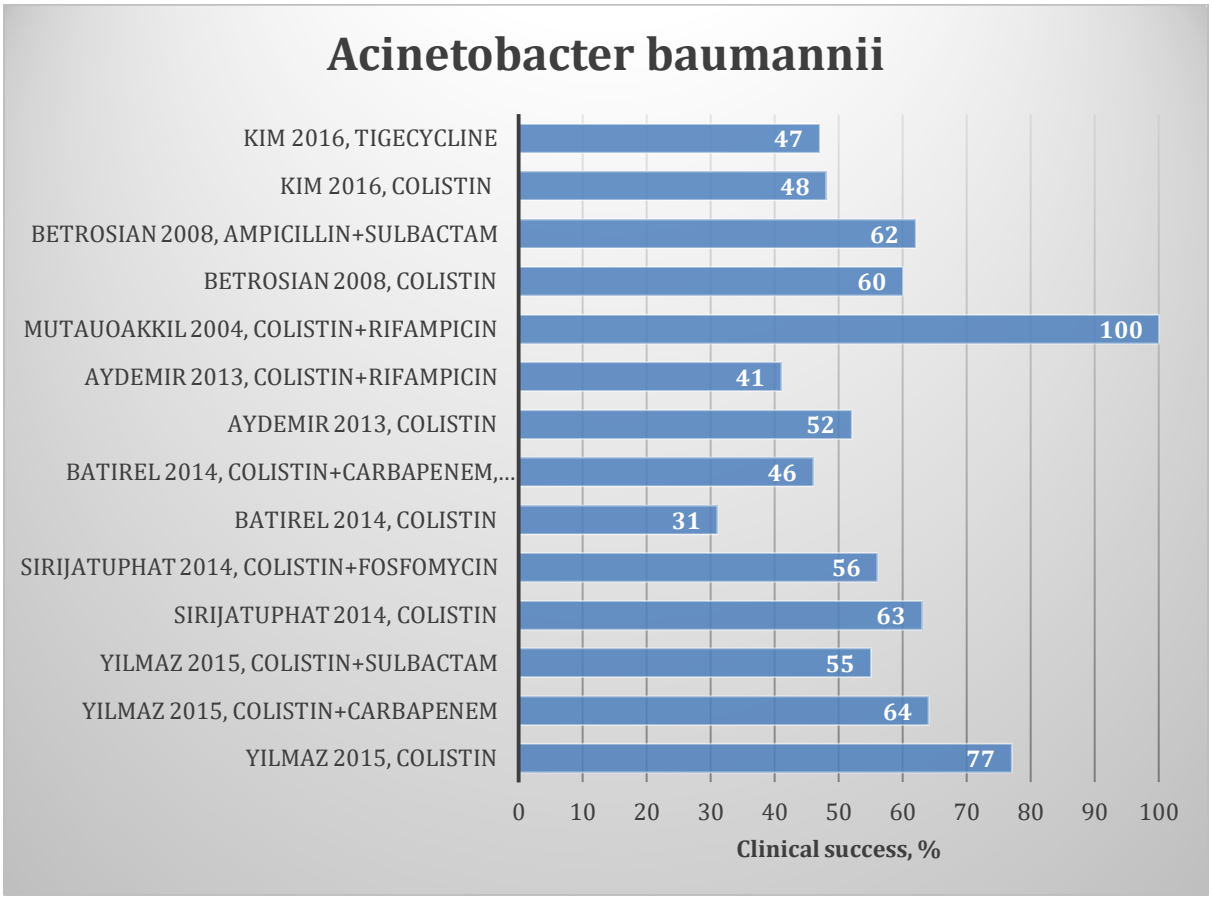
López-cortés et al. investigated 14-day and 30-day all-cause mortality when comparing monotherapy (colistin, carbapenem, tigecycline, sulbactam, tetracycline) with combination therapy (colistin-tigecycline, carbapenem-tigecycline, colistin-carbapenem, colistin-sulbactam, colistin-aminoglycosides, colistin-rifampicin, carbapenem-aminoglycosides, tigecycline-rifampicin, tigecycline-aminoglycosides, colistin-tigecycline-carbapenem-aminoglycosides, colistin-tigecycline-aminoglycosides, and tigecycline-carbapenem-rifampicin) in 101 patients with *A. baumannii* bloodstream infection in various sites. Crude 14-day mortality was 15% and 15% for monotherapy and combination therapy, respectively (relative risk (RR) was 1.03, 95% confidence interval (CI): 0.38-2.77, p=0.95). Crude 30-day mortality was 24% and 24% (RR was 1.03, 95% CI: 0.49-2.16, p=0.94) for monotherapy and combination therapy, respectively (47).

3.3.2. Conclusion for A. baumannii

In terms of clinical success, colistin combination therapy (colistin with carbapenem, sulbactam, fosfomycin, tigecycline, or rifampicin) had no significant advantage to colistin monotherapy (46, 48, 58, 59). Colistin combination therapy had clinical success of 41% to 64%, whereas

colistin monotherapy has clinical success of 31% to 77% (Figure 3). One study had 100% clinical success for colistin-rifampicin treatment of 26 patients admitted to intensive care unit. Controversies were found regarding favorable microbiological success when evaluating colistin monotherapy and colistin in combination with carbapenem (46), sulbactam (48), or rifampicin (59, 62). Therapy with ampicillin/sulbactam did not have a better outcome compared to colistin monotherapy (52). No significant difference in mortality evaluated at 14 days or 30 days for any comparison of treatment was found. Tigecycline (49, 51) showed a positive effect on clinical outcome and microbiological outcome, but more studies comparing colistin with minocycline or tigecycline are needed in order to evaluate the efficacy of treatment options and choice of treatment for patients infected with MDR *A. baumannii*. López-cortés et al. found that in general combination therapy was not superior to monotherapy (47).

Figure 3. Results regarding choice of treatment and clinical success for *A. baumannii*



3.4. S. maltophilia

3.4.1. Results regarding choice of treatment and outcomes for S. maltophilia

We identified two studies that were investigating the success of different treatment options for *S. maltophilia*. Study characteristics and quality are shown in Table 3. A systematic review by Mori et al. (based on studies published up to 2013) reported 100% mortality among 30 patients sustaining hemorrhagic pneumonia by *S. maltophilia*. Treatment options included combination therapy with high-dose co-trimoxazole + fluoroquinolones, high-dose co-trimoxazole monotherapy, fluoroquinolones, and broad-spectrum antibiotics (e.g. vancomycin or carbapenems). Only two patients survived more than one week. Both patients received high-dose cotrimoxazole + fluoroquinolones combination therapy (63). Another systematic review by Falagas et al. (based on 34 studies and 49 patients in total published up to 2008) investigated clinical response for *S. maltophilia* infections treated with other antibiotica than co-trimoxazole. Antibiotic treatment included ciprofloxacin monotherapy or combination therapy (ceftazidime, ceftazidime/gentamicin, amikacin, ticarcillin/clavulanate, piperacillin, tobramycin, and chloramphenicol), ceftriaxone or ceftazidime as mono- or combination therapy (netilmicin, amikacin, ampicillin, ceftriaxone, ceftazidime, tobramycin, and ciprofloxacin), ticarcillin alone or in combination with tobramycin, ticarcillin/clavulate as mono- or combination therapy (teicoplanin and amikacin), levofloxacin, meropenem, gentamicin alone or in combination with piperacillin/tazobactam or chloramphenicol, cefozopran with isepamicin, aztreonam with amoxicillin/clavulanate, minocycline, cefoperazone, imipenem with amikacin and, finally, chloramphenicol in combination with sulfadimidine. Overall, clinical success rates after the administration of alternative treatments ranged from 67%-85%. Treatment with ciprofloxacin as mono- or combination therapy had a clinical success rate of 85% and a mortality rate of 10%. The clinical success rate was 50% and the mortality rate was 17% when patients were treated with ceftriaxone mono- or combination therapy. Four of six patients had clinical success and two of six patients died when treated with ticarcillin or ticarcillin/clavulanate as mono- or combination therapy for infections with *S. maltophilia*. The article concluded that ciprofloxacin, ceftazidime or ceftriaxone, and ticarcillin/clavulanate, alone or in combination with other antibiotics, may be considered as alternative treatment options beyond co-trimoxazole (64).

3.4.2. Conclusion for S. maltophilia

The first-choice antibiotic in the treatment of *S. maltophilia* infection is co-trimoxazole (15 mg/kg/day), however ciprofloxacin, ceftazidime or ceftriaxone, and ticarcillin/clavulanate, alone or in combination with other antibiotics, may be considered as alternative treatment options, beyond co-trimoxazole. Neither of two review studies evaluated or mentioned the duration of treatment.

3.5. ESBL-producing enterobacteriaceae

3.5.1. Results regarding choice of treatment and outcomes for ESBL-producing enterobacteriaceae

Eighteen articles were included, 13 observational studies (65-77) and five randomised studies (43, 78-81). Results, study characteristics, and quality are shown in Table 4. Result regarding antibiotic treatment and clinical success/ moratality are presented in Figure 4 and 5.

Four studies compared treatment with group 1 carbapenems (ertapenem) to treatment with group 2 carbapenems (imipenem/meropenem) (66, 73, 77, 79).

Rattanaumpawan et al. randomized 66 patients who had received any group 2 carbapenem for less than 96 hours into a de-escalation group and a non-de-escalation group. In the intervention (de-escalation) group, the previously-prescribed group 2 carbapenem was de-escalated to ertapenem. In the control (non-de-escalation) group, the group 2 carbapenem was continued. The most common site of infection was urinary tract infection (42%). Clinical and microbiological success in the de-escalation group was 94% and 100% in the de-escalation group and 79% and 96% in the non-de-escalation group. Thus, the de-escalation group was non-inferior to the non-de-escalation group regarding the clinical cure rate (%Δ=14.0 [95% CI: -2.4 - 31.1]), the microbiological eradication rate (%Δ=4.1 [95% CI: -5.0 - 13.4]), and the superimposed infection rate (%Δ= -16.5 [95% CI: -38.4 - 5.3]). 28-day mortality was evaluated and found that 9.4% and 29.4% (p=0.05) of patients died in the de-escalation group and non-de-escalation group, respectively (79).

In Lee et al. (2011), 30-day crude mortality was 18% in the group treated with group 1 carbapenems and 16% in the group treated with group 2 carbapenems (p=1.0) (73).

In Collins et al., 127 patients who were treated with either group 1 or group 2 carbapenems as empirical therapy was evaluated in regard to mortality. 6.1% and 18% (odds ratio [OR] 0.29 (95% CI: 0.08 – 1.0), p=0.05) of patients died during hospital stay and 12% and 33% (OR 0.38

(95% CI: 0.14 – 0.99), p=0.5) died within 90 days after being treated with either group 1 or group 2 carbapenems as empirical therapy, respectively (77).

Thus, no significant difference was seen in clinical success (79) or mortality (73, 77, 79) for treatment with either group 1 or group 2 carbapenems.

However, both empirical and targeted treatment with ertapenem compared to other carbapenems (imipenem, meropenem, or doripenem) significantly lowered the 30-day mortality rate (3% vs. 23%, p=0.01 and 9% vs. 17%, p=0.01) (66). The adjusted HR for 30-day mortality of targeted therapy with ertapenem and other carbapenems showed that interactions were not significant (adjusted HR 0.93 (95% CI: 0.43 – 2.03), p=0.86), factors reported as being adjusted for, can be found in Table 4) (66). Looking at clinical success, Gutierrez-Gutierrez et al. found that empirical therapy with ertapenem compared to other carbapenems did not significantly differ (91% vs. 76%, p=0.06), but targeted treatment with ertapenem compared to other carbapenems showed results in favor of ertapenem (90% vs. 83%, p=0.02). Adjusted OR for targeted therapy with ertapenem was 1.87 (95% CI: 0.24 – 20.08, p=0.58). Patients in the targeted therapy group were matched with patients who received treatment with other carbapenems based on propensity score. Results regarding propensity matched cohort as shown in Table 4.

Lee et al. (2012) also evaluated treatment with carbapenems defined as appropriate treatment, where the causative isolate was susceptible in vitro to the prescribed drug, against inappropriate therapy with carbapenems among 251 patients with bacteremia caused by ESBL-producing *E. coli* and *K. pneumoniae* isolates. A significant reduction in sepsis-related mortality was found in patients receiving appropriate (11%) rather than inappropriate therapy (38%) with carbapenems (p=0.002), irrespective of ertapenem, imipenem, or meropenem therapy (74).

Bassetti et al. showed that treating ventilator-associated pneumonia with ertapenem had a clinical and microbiological success of 80% and 75%, respectively. Bassetti et al. did not include any comparison treatment group in their study (82).

When comparing carbapenems to other specific treatment options, no significance was seen in 30-day mortality for treatment with fluoroquinolones compared to carbapenems (8% vs. 23%, p=0.12) (76). The same tendency was seen in the same study when comparing patients treated with fluoroquinolones to propensity-matched patients in the carbapenem group (OR 4.53 (95% CI: 0.98 – 21.00), p=0.05) (76). Patients treated with cefepime were more likely to die within 30 days (OR 7.1 (95% CI: 2.50 – 20.3), p<0.001) than patients treated with carbapenems (75).

A single study (65) compared group 1 carbapenems with piperacillin-tazobactam and found no significance in in-hospital mortality (13% vs. 4%, p=0.059) or microbiological success (95% vs. 96%, p=1.0) among 150 patients with acute pyelonephritis.

Goetheart et al. compared group 2 carbapenems (imipenem/meropenem), as combination therapy or monotherapy, with other antibiotic treatment options against treatment with cefepime (68). Solomkin et al. compared ceftolozane/tazobactam+metronidazole with meropenem treatment (81) and Carmeli et al. investigated ceftazidime-avibactam against best available treatment including group 2 carbapenems as monotherapy (43). Goethart et al. (68) found that patients treated with cefepime did not have a significantly better outcome in terms of clinical success (62% vs. 70%, p=0.59), microbiological success (14% vs. 22%, p=0.76), or 30-day mortality rates (33% vs. 26%, p=0.44) when compared to imipenem/meropenem. Solomkin et al. (81) found that treatment with ceftolozane-tazobactam+metronidazole did not improve clinical success when compared to meropenem (95.8% vs. 88.5%). Carmeli et al. (43) investigated ceftazidime-avibactam compared to best available treatment (including imipenem [53%], meropenem [34%], and other) in patients with urinary tract infection or cIAI caused by *P. aeruginosa* or ESBL-producing *enterobacteriaceae*. Total of 263 patients had urinary tract infection and 20 had cIAI due to ESBL-producing *enterobacteriaceae*. Clinical success in patients with ESBL-producing *enterobacteriaceae* specific urinary tract infection occurred in 120 of 131 (92%) patients treated with ceftazidime-avibactam and 124 of 132 (94%) patients treated with best available treatment. Microbiological success in patients with urinary tract infection was favorable in 107 of 131 (82%) cases and 85 of 132 (65%) cases for ceftazidime-avibactam compared to best available treatment, respectively. Patients with cIAI had a favorable clinical success in 8 of 9 (89%) cases and 5 of 11 (45%) cases for ceftazidime-avibactam compared to best available treatment, respectively.

Other treatment options included piperacillin-tazobactam vs. ertapenem vs. cefepime (78), ceftolozane/tazobactam vs. levofloxacin and ceftolozane/tazobactam vs. ertapenem (80), ceftazidime vs. imipenem/cilastatin vs. cefoperazone/sulbactam (70).

Seo et al. (78) showed, among 72 patients with urinary tract infection, a significant difference in clinical success when treating patients with piperacillin-tazobactam vs. ertapenem vs. cefepime (94% vs. 97% vs. 33%, p<0.001). However, treatment with cefepime was ended during the study period due to high treatment failure in 4 if 6 cases (67%). Treatment with piperacillin/tazobactam and ertapenem was completed and both had a high rate of clinical success (94% vs. 97%, p=0.50). Both piperacillin/tazobactam and ertapenem groups showed the same outcome when looking at microbiological (97%) and 28-day mortality rates (6%) (78). A phase III clinical trial (80) investigated patients with urinary tract infection randomly assigned to treatment with either ceftolozane-tazobactam or levofloxacin and patients with cIAI randomly

assigned to treatment with either ceftolozane-tazobactam or ertapenem. Significant better clinical success was seen in treating urinary tract infection with ceftolozane/tazobactam compared to levofloxacin (98% and 83%, p=0.01). Clinical success in patients with cIAI was 96% for ceftolozane/tazobactam and 89% for carbapenem (p>0.05). Microbiological success was 80% compared to 63% for ceftolozane/tazobactam compared to pooled data on other treatment.

Bin et al. found similar clinical success in treatment with ceftazidime (86%) imipenem/cilastatin (88%) and cefoperazone/sulbactam (71%) (p=0.64) (70). No patients treated with any of the abovementioned antibiotics died within the study period.

Treatment with cefoxitin was retrospectively evaluated in 33 patients with infection due to ESBL-producing *enterobacteriaceae and* 91% and 83% had a favorable clinical outcome at follow-up on the 3rd and 14th day after initiating treatment, respectively (69). Tasbakan et al. (71) retrospectively looked into treatment with nitrofurantoin in 75 patients with lower urinary tract infection and reported that clinical and microbiological success rates were 69% and 68%, respectively. Amikacin was used to treat 36 patients with positive urine cultures for ESBL-producing *enterobacteriaceae* or *K. pneumoniae* and showed clinical success in 97% of patients whereas microbiological success was seen in 92%, 97.1%, and 94.1% of cases on the 3rd day of treatment, at end of treatment, and 7-10 days after treatment (72).

Figure 4. Results regarding choice of treatment and clinical success for *ESBL-producing Enterobacteriaceae*

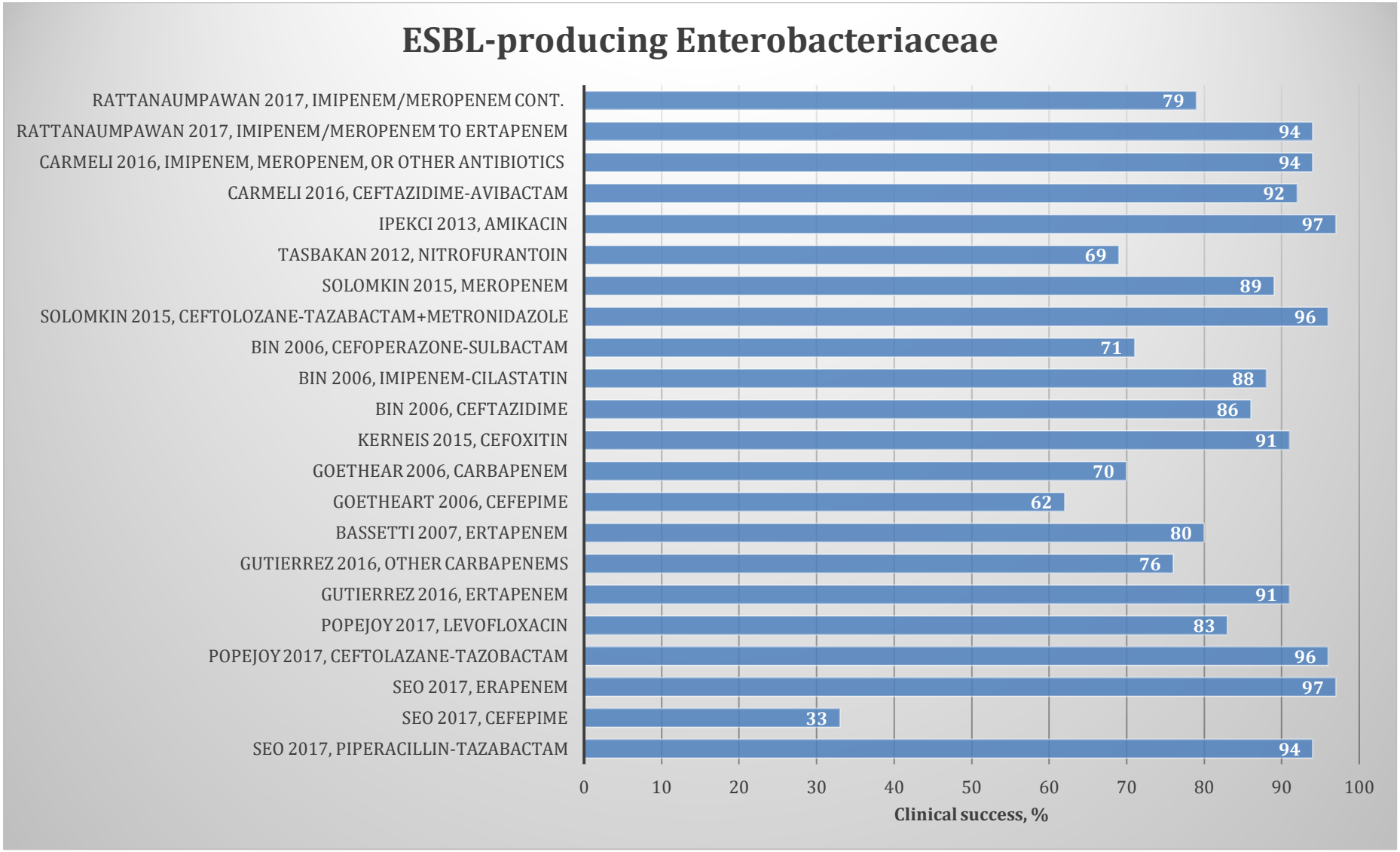
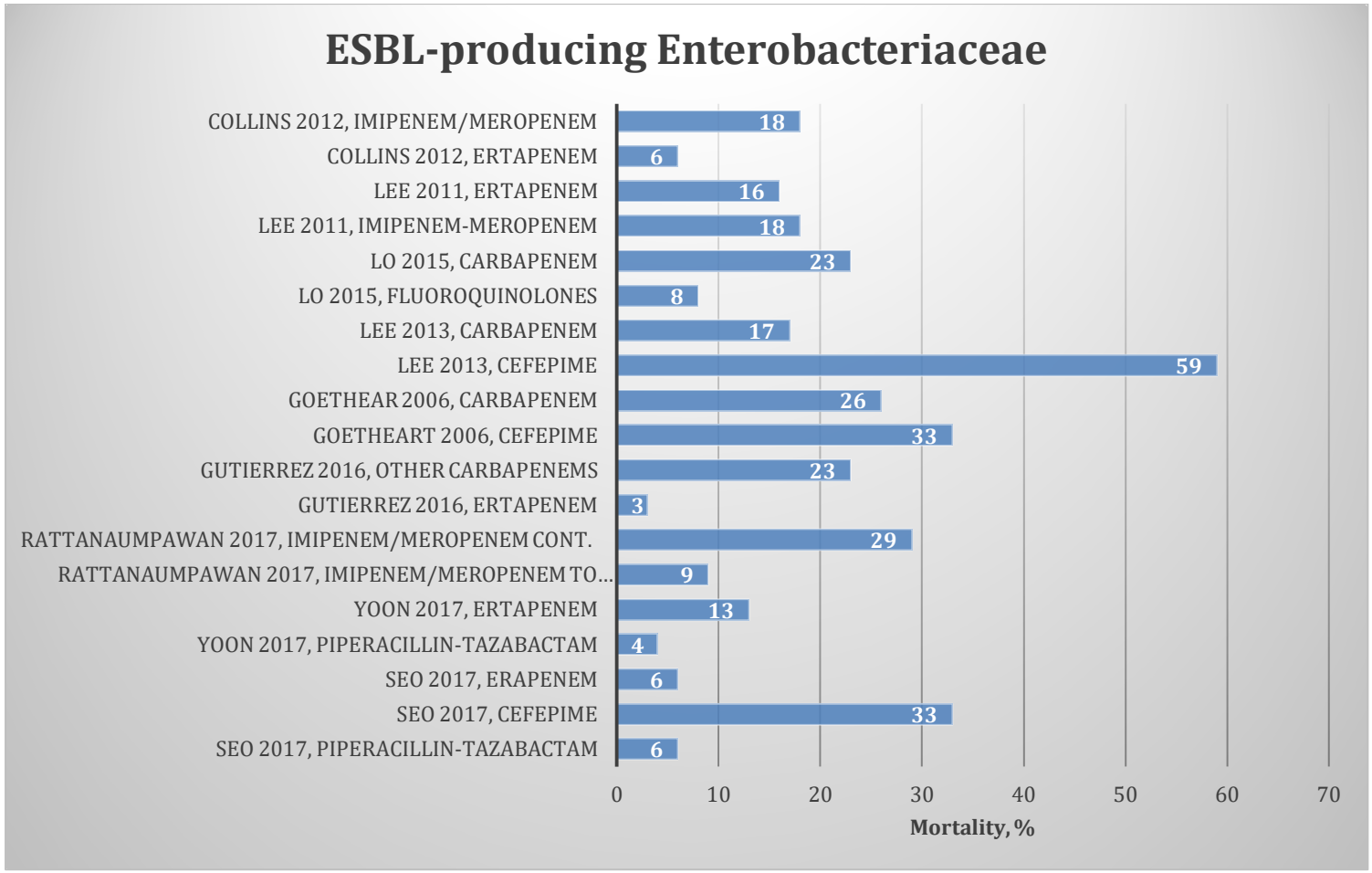


Figure 5. Results regarding choice of treatment and mortality for *ESBL-producing Enterobacteriaceae*



3.5.2. Conclusion for ESBL-producing enterobacteriaceae

Treatment with carbapenems (inkl. ertapenem, meropenem) based on in vitro susceptibility of the causative isolate significantly reduced sepsis-related mortality (74) for patients receiving appropriate therapy. Piperacillin/tazobactam, cefepime, ceftolozane/tazobactam, levofloxacin, fluoroquinolones, ceftolozane/tazobactam, and imipenem/cilastatin were investigated as alternative treatment options to carbapenems. Seven studies found similar effects between investigated treatments compared to carbapenems in mortality (65, 68, 76, 78), clinical success (43, 68, 81, 83), and microbiological success (68, 83). Clinical success and mortality was not related to cefepime treatment.

Regarding the clinical success, the following drugs alone or in combination had success rate of more than 90%: piperacillin-tazabactam, ceftolazane-tazabactam, erapenem, ertapenem, cefoxitin, ceftolozane-tazabactam in addition to metronidazole, amikacin, and cetazidime-avibactam. In addition, following drugs had 80% to 90% clinical success: levofloxacin, ceftazidime, imipenem-cilastatin, and meropenem.

Mortality was less than 10% for piperacillin-tazabactam, erapenem, ertapenem (to studies), and fluoroquinolones. However, more than 10% mortality was observed for following antibiotics: cefepime, ertapenem (to studies), imipenem/meropenem, and carbapenem.

Three studies had no comparing group and found that cefoxitin (69), nitrofurantoin (71), and amikacin (70) had a favorable clinical and microbiological outcome, but further investigation is needed in order to compare the clinical effect and safety.

Thus, due to variation in infection site, sample size, and number of patients evaluated for specific antibiotics, no firm recommendation can be made on any antibiotic as beneficial in relation to another antibiotic. However, several antibiotics have good clinical success with low mortality.

4. Discussion

In summary, we identified 42 articles, which report on clinical success, microbiological success, and/or mortality in relation to different treatment options for four most common MDR Gram-negative bacteria, *E. coli*, *P. aeruginosa*, *A. baumannii*, *S. maltophilia*, or ESBL-producing *enterobacteriaceae*. A variety of antibiotics have been used for a constellation of MDR Gram-negative bacteria. We did not find robust evidence for any of the four bacteria that would lead to a firm recommendation of one specific antibiotic over another or for monotherapy over

combination therapy. However, some treatment options might be more beneficial for low or high life-threatening infections.

The most common option for treatment of *P. aeruginosa* infections was intravenous colistin regardless of infection site. Monotherapy and different colistin combination therapies were used with clinical and microbiological success between 70% and 100% depending on site and severity of infection and antibiotic used. For treatment of *A. baumannii* intravenous colistin was also the first drug of choice. Clinical success and mortality were similar in cases treated with colistin combination therapy compared to monotherapy. Contradictory results were found when comparing combination vs. monotherapy in regard to microbiological success. The first-choice antibiotic in the treatment of *S. maltophilia* infection is co-trimoxazole. Alternatives included ciprofloxacin, ceftazidime, and ceftriaxone or ticarcillin/clavulanate alone or in combination.

For the treatment of ESBL-producing *enterobacteriaceae*, the most commonly used antibiotics were carbapenems. The effect of group 1 carbapenems (ertapenem) compared to group 2 carbapenems (imipenem, meropenem or doripenem) was contradictory in regard to reduction in mortality. No difference was seen between group 1 and 2 carbapenems in terms of clinical and microbiological success but de-escalated to ertapenem could be beneficial in less life-threatening conditions. Piperacillin-tazabactam as alternative therapy and ertapenem showed good clinical success with low mortality.

Strengths and limitations

Our study has several limitations. There are limitations of this review process due to limitations of the search strategy as we only used the MEDLINE database for the literature search, which may not cover all published articles. As we limited our search to the English language, and since some non-English speaking countries may have higher problems with MDR bacteria compared with English speaking countries, we may have missed relevant articles published in other languages. However, due to the major shift towards publication of studies in English, the extent and effects of language bias may have recently been reduced. Our search strategy may have missed relevant articles as the term “multi resistant” used in the search string may not cover all articles concerning multi resistant bacteria since synonyms are used for MDR. Lack of a standard definition of MDR results in a great diversity exists when defining MDR (2, 84). Consequently, the use of the term MDR in the included studies may not cover the same bacteria and drug resistance. In an attempt to avoid excluding relevant literature, different synonyms were accepted as MDR (e.g. carbapenem-resistance and XDR) and

all references in the included articles were screened for eligibility. We recomend to use European Centre for Disease Prevention and Control and the Centers for Disease Control and Prevention (CDC), existing standardized international terminology for MDR bacteria.

Risk of publication bias is another limitation of this review. It is likely that studies reporting on antibiotic treatment with high clinical and microbiological success are more likely published. Around 50% of studies are estimated to be unpublished, including a majority of studies with less significant or negative results. Further, 36% of the included studies were found by scanning reference lists from published articles which might have caused notation bias.

In general, the study qualities of the included articles were fluctuating. 20% (n=8) were poor in terms of quality, 73% (n=30) were fair, while only 7% (n=3) were good quality studies. The included studies were heterogeneous in terms of study design, patient population, site of infection, choice of antibiotic treatment, duration of follow-up period, and the outcome definitions, making it difficult to compare the different treatments and combinations of antibiotics used. Subsequently, it was impossible to pool results and perform the meta-analysis. Most patients included in the studies were critically ill, often comorbid, and admitted to an intensive care unit: facts which may underestimate the specific effect on mortality of a certain antibiotic treatment against MDR organisms. Some studies included patients irrespectively of site of infection, whereas other studies included studies with specific infections such as pneumonia or urinary tract infection. The severity of these infections is different which again can affect the antibiotic treatment-related outcome. In addition, the studies were often based on small sample sizes reducing the ability to find any effect difference and to consider confounder adjustment and multivariate regression analysis. Only few studies (44, 47, 51, 52, 54, 55, 62, 65, 66, 75, 77, 81) presented a sample size estimation and adhered to it.

The results from this systematic review may not be applicable for all countries since the majority of included studies are from non-comparable countries with different healthcare systems and extent of use of antibiotics.

Adverse events were not a focus point of this study but are an important aspect in the treatment of patients since dosage adjustments must be considered and might have affected the results in this review in terms of clinical success, bacteriological success, and mortality towards no correlation. Another perspective is the fact that patients infected with the studied bacteria are often critically ill which makes it important to have extensive knowledge of the effects and side effects of the treatment of choice. The included studies that conducted a multivariate analysis often emphasized the confounding effect of the severity of illness and patients' comorbidity.

Some of the treatments can be administered orally. We found a single study where nitrofurantoin was administered orally (71). Most intensive care unit patients are treated with intravenous due to severity of their condition but when recovering most patients can be transitioned to oral administration of antibiotics, this makes it easier for the patient to administer at home, and cheaper for society, but further studies must be made in order to establish effect and cost-benefit of antibiotic treatment administered intravenously vs. oral administration.

To the best of our knowledge, no other systematic reviews have been able to create a specific guideline for treatment of MDR Gram-negative infections. A prior systematic review suggested that colistin combination therapy may be prefered to colistin monotherapy for severely ill patients infected with MDR *A. baumannii*, but no firm evidence could be found (85). Another systematic review proposed treating carbapenem-resistant ESBL-producing *enterobacteriaceae* and *P. aeruginosa* with carbapenem plus either colistin or tigecycline combination therapy in low-level resistant infections and colistin-tigecycline combination therapy in high-level resistant infections (86). Similar findings were published by Rafailidis et al. in 2014 (34). The authors concluded that carbapenem in combination with colistin or high-dose tigecycline or aminoglycosides could be used for treatment of carbapenem-resistant ESBL in cases where the minimum inhibitory concentration range of carbapenem is ≤8 mg/l (34).

Conclusion

To the best of our knowledge, this is the newest systematic review that attempts to critically appraise current evidence for the treatment of MDR *P. aeruginosa*, *A. baumannii*, *S. maltophilia*, and ESBL-producing *enterobacteriaceae* and create a standard guideline based on these results. A guideline could not me made due to low-quality evidence and heterogeneous studies. A consequence of the lack of current guidelines became apparent in the heterogeneity of the suggested treatments. As of now, there is an immense need for further research comparing specific and comparable antimicrobial treatment options in order to conduct a meta-analysis and create an evidence-based guideline. Still, there are some antibiotic options identified for each MDR bacteria with good clinical success and low mortality.

Study 1 – Systematic review, Tables 1-4

Table 1. Choice of treatment and outcomes for Pseudomonas aeruginosa

Pseudomonas aeruginosa																
Study characteristics																**Study quality**
Source	**Study type**	**Publication year and country of origin**	**Study period**	**Setting**	**Inclusion criteria**	**No. of patients (incl/all)**	**Mean age (years)**	**Antimicrobial treatment**	**Route**	**Follow-up**	**Site of infection**	**Outcomes evaluated**	**Outcome measures**	**Results**	**Factors reported as being adjusted for**	**Quality assessment**
Sorli et al	Prospective observational cohort study	2017, Spain	2009-2013	H	All patients with microbiologically documented infections due to XDR *p. aeruginosa* and were administered colistin for at least 72 hours	91	age range: 24-88	Colistin	IV	Until discharge or death	Any	Clinical success 30-day all-cause mortality	absolute value	**Clinical success** 79.1% **30-day all-cause mortality** 30.8%	Male sex, age, APACHE score, Comorbidities, Charlson score, McCabe score, severe sepsis, department of hospitalization, CMS daily dose Css (mg/mL), Css > 1.25 (mg/mL), Css/MIC, AKI at day 7, AKI at the EOT, Length of stay	Fair
Wright et al	Randomised double-blind, placebo-controlled phase I/II clinical trial	2009, United Kingdom	NR	OC	Longstanding, antibiotic resistant, aural discharge due to infection exclusively or predominantly by *p. aeruginosa*.	24	56.7	Biophage-PA or placebo	Injection into one ear	day 7, 21 and 42	Ear	Physician reported VAS Patient reported VAS Pseudomonas count	mean reduction as percentage of day 0	**Mean combined VAS** Biophage-PA: 50% reduction Placebo: 20% reduction **Pseudomonas count** Biophage PA day 7: 56.9% day 21: 17.4% (p=0.0001) day 42: 23.9% (p=0.016) Placebo	none	Fair

														day 7: 141.6% (p day 21: 78.5% day 42: 108.9%		
Montero et al	Retrospective observational study	2009, Spain	1997-2006	H	Patients who received treatment with colistin for more than 3 days following an episode of active infection with MDR *p. aeruginosa*	121	65.34 (± 14.1)	colistin or colistin associated with aminoglycosides, **β**-lactams, quinolones or carbapenems	IV and IV+Nb	NR	Any	Clinical success	Absolute value	**Clinical success** C: 73% C+aminoglycosides 71.9% C+**β**-lactam 72% C+quinolones 75% C+carbapenem 65.5%	Site of infection, hypertension, chronic renal insufficiency, diabetes mellitus, Aminoglycosides, ACE-inhibitors	Poor
Carmeli et al*	Randomized phase III study	2016, Worldwide including 16 countries	2013-2014	H	Patients aged 18-90 years with ongoing symptoms of either complicated UTI or pyelonephritis or cIAI at the time of screening and an isolated causative Gram-negative ceftazidime-resistant pathogen could be included regardless of previous antibiotic therapy. Patients who had received previous antibacterial agents that were effective in vitro against the isolated pathogen (based on the known susceptibility profile of the organism) were required to have worsening of objective symptoms or signs of infection after 48 h or longer of therapy, or absence of improvement after 72 hours or longer of therapy.	21/333	64.3 (± 14.6) and 61.3 (±15.3) and 49.9 (±16.1) and 68.4 (±11.1)	CA or BAT	IV	TOC visit 7-10 days after last infusion of treatment therapy	UTI cIAI	Clinical success Microbiological success	Absolut value	**Clinical success in UTI** CA: 86% BAT: 100% **Microbiological success in UTI** CA: 79% BA: 60% **Clinical success in cIAI** CA: 100% BAT: 100% **Microbiological success in cIAI** BA: 100% CA: 100%	none	Fair

Abbreviations: No. = number, incl = included patients with relevant infection, H = hospital setting, OC = outpatient clinic, XDR = extended drug resistant, CA = ceftazidime-avibactam, BAT = Best available treatment, IV = intravenous, Nb = nebulized, NR = not reported, TOC = test-of-cure, UTI = urine tract infection, cIAI = complicated intra abdominal infection, VAS= visual analogue scale, C = colistin, APACHE = Acute Physiology And Chronic Health Evaluation II, CMS = colistimethate sodium, Css = colistin steady state, MIC = minimal inhibitory concentration, AKI = acute kidney injury, EOT = end of treatment
*article including treatment and outcome for more than one bacteria therefore mentioned in more tables, but only included once in the study.
Greyscale = studies comparing treatment options

Table 2. Choice of treatment and outcomes for Acinetobacter baumannii

Acinetobacter baumannii																
Study characteristics																**Study quality**
Source	**Study type**	**Publication year and country of origin**	**Study period**	**Setting**	**Inclusion criteria**	**No. of patients (incl/all)**	**Mean age (years)**	**Antimicrobial treatment**	**Route**	**Follow-up**	**Site of infection**	**Outcomes evaluated**	**Outcome measures**	**Results**	**Factors reported as being adjusted for**	**Quality assessment**
Alvarez-Marin et al	Prospective, observational cohort study	2016, Spain	2010-2011	ICU	Adult patients admitted to the ICU and requiring invasive mechanical ventilation for more than 48 hours, and having at least one culture of trachea-bronchial aspirate with *A. baumanni*i isolation.	100	51 (43.5-69.5)	Colistin	NR	30 days or until death	airway	30-day all-cause mortality	absolute value	**30-day all cause mortality** 14%	Acute kidney injury, bacteremia	Fair
Bremmer et al	Retrospective observational study	2016, USA	2009-2013	H	Patients who had pneumonia or bacteremia and received ≥ 48 hours of an antibiotic combination analyzed by the checkerboard analysis	18	59.5	Treatment based on checkerboard findings (Ti+C, Do+C, Mi+C, Do+C+Ti)	NR	a maximum of 30 days	airway BSI	Clinical success Microbiological success 30-day all-cause mortality	absolute value	**Clinical success** Group 1[A] 50% Group 2[B] 30% p = 0.63 **Microbiological success** Group 1[A] 88% Group 2[B] 30% p = 0.02 **30-day all-cause mortality** Gruop 1[A] 38% Group 2[B] 60% p = 0.63	none	Poor

Yilmaz et al	Retrospective observational study	2015, Turkey	2011-2013	ICU	Patients diagnosed with VAP due to MDR or XDR *A.baumannii* and who received colistin treatment	70	59.8 (± 21.5) and 59.6 (± 20.5) and 70.6 (± 14.7)	Colistin, C-carbapenem C-sulbactam	IV	a maximum of 28 days	airway	Clinical success Microbiological success Crude mortality	absolute value	**Clinical success** C 76.5% C-carbapenem 63.6% C-sulbactam 55% $p^1 = 0.35$ $p^2 = 0.53$ **Microbiological success** C 52.9% C-carbapenem 63.6%% C-sulbactam 60%% $p^1 = 0.23$ $p^2 = 0.16$ **28-day all-cause mortality** C: 41.2% C-carbapenem 48.5% C-sulbactam 70% $p^1 = 0.53$ $p^2 = 0.21$	Comorbidity, clinical response, SAPS2, age, duration of treatment	Fair
Sirijatuphat et al	Preliminary open-label randomized controlled study	2014, Thailand	2010-2011	H	hospitalized adults age 18 years who developed CR A. baumannii infection and required treatment with colistin.	94	67.4 (± 17.2) and 69.2 (± 16.3)	Colistin C-fosfomycin	IV	72 h, end of treatment and 28 days after treatment	any	Clinical success Microbiological success 28-day all-cause mortality	absolute value	**Clinical success** C: 62.8% C-Fo = 56.4% p = 0.654 **Microbiological success** C: 100% C-Fo: 85.5% p = 0.023 **28-day all-cause mortality** C: 53.8% C-Fo: 44.2% p = 0.507	none	Poor

López-cortés et al	Prospective, observational cohort study	2014, Spain	2010	H	Patients with infection caused by *A. baumannii*, sepsis criteria were present; and the patient received treatment with at least one drug active in vitro for at least 48 hours following the clinical diagnosis of infection.	101	60 (52-75)	monotherapy (C, CP, Ti, SB, tetracycline) or combination therapy (C-Ti, CB-Ti, C-CB, C-SB, C-AG, C-R, CB-AG, Ti-R, Ti-AG, C-Ti-CB-AG, C-Ti-AG, Ti-CB-R)	NR	a maximum of 30 days	BSI	30-day all-cause mortality 14-day all-cause mortality	RR	**30-day all-cause mortality** monotherapy: 23.5% combination therapy: 24.2% RR = 1.03; 95%CI 0.49-2.16 p = 0.94 **14-day all-cause mortality** monotherapy: 14.7% combination therapy: 15.2% RR = 1.03 95% CI 0.38–2.77 p = 0.95	Age-weighted Charlson comorbidity index, Pitt bacteremia score, empirical treatment	Fair
Batirel et al	Retrospective observational study	2014, Turkey	2009-2012	H	Patients > 18 y with a confirmed XDR a. baumannii (isolation of XDR *A. baumannii* from ≥2 separate sets of hemoculture bloodstream infection treated with colistin monotherapy or colistin-based combination therapy intravenously for ≥72 hours.	250	59.1 (± 19.6) and 58.3 (± 20.5)	Colistin or Colistin combination therapy (C-carbapenem, C-sulbactam, C-other agents)	IV	C-mono: 45.8 days (9–223) C-comb: 56.9 (5–497)	BSI	14-day survival Clinical success Microbiological success	absolute value	**14-day survival** Monotherapy: 55.5% Combination therapy: 68.2% p = 0.14 **Clinical success** monotherapy: 30.6% combination therapy: 46.3% p = 0.19 **Microbiological success** monotherapy: 79.9% combination therapy: 56.6% p = 0.001	Age, hospital stay prior to XDR *A. baumannii* BSI, ICU stay prior to XDR *A. baumannii* BSI, Pitt bacteremia score, APACHE II score, Charlson comorbidity index	Fair

Durante-mangoni et al	Phase III random-ized clini-cal trial.	2013, Italy	NR	ICU	Adult subjects (>18 years) with microbiologic evi-dence of a life-threatening nosocomial infection due to XDR *A. baumannii*	210	62 (±15.4)	Colistin or colistin-rifam-picin	IV	a maximum of 30 days	air-way BSI abdo-minal	Micro-biologi-cal suc-cess 30-day all-cause mortal-ity Infec-tion re-lated morta-lity	abso-lute value	**Microbiolog-ical success** C: 44.8% C-Ri: 60.6% p = 0.03 **30-day all-cause mor-tality** C: 42.9% C-Ri: 43.3% p = 0.93 **Infection re-lated mortal-ity** C: 26.6% C-Ri: 21.2% p = 0.29	Demographic (age and sex) and clini-cal (source of infec-tion, admission type, concomitant infections, SAPS II score, MIC for rifampicin, co-morbidity score)	Fair
Ayde-mir et al	Randomi-zed study	2013, Turkey	2011-2012	ICU	Patients aged > 18 years with a diagnosis of VAP whose culture and antimi-crobial susceptibility results indicated infection with car-bapenem-resistant *A. bau-mannii* within 48 hours after onset of VAP; and patients whose legal representatives accepted and signed the in-formed consent form.	43	61 (± 20)	Colistin or colistin-rifam-picin	C: IV R: NG	until death or discharge	air-way	Clinical success Micro-biologi-cal suc-cess	abso-lute value	**Clinical suc-cess** C: 52.4% C-Ri: 40.9% p = 0.654 **Microbio-logical suc-cess** C: 71.4% C-Ri: 59.1% p = 0.597	None	Fair
Vasilev et al	Phase III non- com-parative study (ob-serva-tional)	2008, England	NR	H	Patients with clinical evi-dence of infection and a confirmed baseline culture of a Gram-negative patho-gen(s) that was susceptible to tigecycline, sufficient information available to al-low a determination of mi-crobiological response and completed an evaluation for efficacy.	115	55.4 (± 15.89) and 50.75 (±21.00) and 56.20 (±16.51)	Tigecycline	IV	TOC (after 12-37 days)	BSI air-ways abdo-minal skin	Clinical success Micro-biologi-cal suc-cess	abso-lute value	**Clinical suc-cess** 72.2% (95% CI: 54.8–85.8) **Microbiolog-ical success** 66.7% (95% CI: 13.7–78.8)	None	Fair
Saballs et al	Prospec-tive fol-low-up study (observa-tional)	2006, Spain	2000-2001	ICU	Patients with serious infec-tions due to carbapenem re-sistant *A. baumannii*	10	55.2	Rifampicin-imipenem	IV	NR	any	Clinical success Crude morta-lity	abso-lute value	**Clinical suc-cess** 70% **Crude mor-tality** 30%	None	Fair

Mutauoakkil et al	Observational study	2005, Morocco	2004	ICU	The presence of at least two of fever (>38.3 °C), leukocytosis or leukopenia, purulent bronchial secretions, and a new or persistent infiltrate on chest radiography. All the strains of *A. baumannii* were resistant to all ántibiotics apart from colistin	26	42.58 (±18.29)	colistin-rifampicin	IV aerosolized 1 case intrathecal	NR	airway BSI meninges	Clinical success	NR	**Clinical success** 100%	None	Fair
Betrosian et al (2008)	Randomized prospective cohort study	2008, Greece	1 year period	ICU	All mechanical ventilated patients (>72 hours) who developed VAP due to MDR A. *baumannii* isolated from bronchoscopic bronchoalveolar lavage.	28	67 (±9) and 72 (±5)	Colistin or ampicillin-sulbactam	IV	5 days after treatment initiation and a maximum of 28 days	airway	Clinical success Bacteriological success 14-day mortality All-cause 28-day mortality	absolute value	**Clinical success** Colistin: 60% Ampicilin-SB: 61.5% p = NS **Microbiological success** Colistin: 66.6% Ampicillin-SB: 61.5% p < 0.2 **14-day mortality** Colistin: 20% Ampicilin-SB: 15.3% p = NS **All-cause 28-day mortality** Colistin: 33% Ampicillin-SB: 30% p = NS	None	Poor
Betrosian et al (2006)	Randomized prospective trial	2006	2004-2006	ICU	All patients mechanically ventilated for 72 hours with positive tracheal aspirates for *A. baumannii*	27	67 (±4.5) and 72 (±2.8)	ampicillin-sulbactam 18/9 g/day or ampicillin-sulbactam 21/12 g/day	NR	5 days after treatment initiation and a maximum of 30 days	airway	Clinical success Microbiological success, 14-day mortality All-cause	absolute value	**Clinical success** Overall: 66.7% Group A[C]: 9/14 (64.2%) Group B[D]: 9/13 (69.2%) p=0.785	None	Fair

												28-days mortality.		**Microbiological success** Overall: 77.8% Group A[C]: 12/14 (85.7%) Group B[D]: 9/13 (69.2%) p=0.303 **14-day mortality** Overall: 25.9% Group A[C]: 3/14 (21.4%) Group B[D]: 4/13 (30.8%) p =0.580 **All-cause 30-day mortality** Overall: 48.1%. Group A[C]: 6/14 (42.9%) Group B[D]: 7/13 (53.8%) p=0.568		
Ye et al	Retrospective observational study	2011, Taiwan	2007-2010	ICU	Adult patients (≥18 years old) who received tigecycline treatment for pneumonia involving MDR *A. Baumannii*	112	70 (±15.5)	Tigecycline	IV	a maximum of 30 days	airway	Clinical success 30-day mortality	absolute value	**Clinical success** 60.3% **30-day mortality** 36.2%	Female gender, concomitant diseases, APACHE II score, mechanical ventilation, bilateral pneumonia, multisite infection, monomicrobial MDR *A. baumannii* pneumonia, duration of treatment	Fair
Kim et al	Retrospective observational study	2016 Korea	2009-2010	ICU	Adult patients (≥20 years old) who had a confirmed diagnosis of hospital acquired pneumonia) or VAP caused by MDR/XDR *A. baumannii* and received either tigecycline or colistin mono-/combination therapy as the initial anti-	70	72 (64-76) and 67 (57-75)	Tigecycline or colistin	IV	a maximum of 30 days	airway	Clinical success Microbiological success 30-day mortality	absolute value	**Clinical success** Tigecycline 47% Colistin: 48% **Microbiological success** Tigecycline:	Solid cancer, recent chemotherapy, steroid use, SOFA score, radiologic score, MDR/XDR *A. baumanni*i bacteremia, neutropenia	Fair

					MDR/XDRAB treatment for at least 3 days.									23% Colistin: 30% **30-day mortality** Tigecycline: 33% Colistin: 30%		
Goff et al	Retrospective observational study	2014 USA	2010-2013	H	Adult patients (age ≥18 and <89 years) with a culture positive for MDR *A. baumannii* defined as nonsusceptible to ≥1 agent in ≥3 antimicrobial categories (excluding minocycline). Culture with in vitro susceptibility to minocycline and minocycline administered within 72 hours of the onset of MDR *A. baumannii* infection, and receipt of minocycline for ≥48 hours	55	56 (23-85)	Minocycline or. Minocycline in combination with other antibiotics (Colistin, doripenem, ampicillin/ sulbactam)	IV	NR	any	Clinical success Microbiological success	absolute value	**Clinical success** Minocycline: 100% Minocycline-comb: 71.15% **Microbiological success** Minocycline: 100% Minocycline comb: 76.92%	none	Fair
Cheng et al	Prospective observational study	2015 Taiwan	2010-2013	H	Patients who had XDR *A. baumannii* genospecies 2 bacteremia and were prescribed parenteral colistin in combination with either tigecycline or carbapenem within 48 hours of culture report. Only the first episode of bacteremia was included	55	62 (44-73) and 62 (45-81)	C-tigecycline or C-carbapenem	IV	blood cultures on day 3 and 7 until death or discharge	BSI	14-day all-cause mortality All-cause in-hospital mortality	absolute values HR	**14-day all-cause mortality** C-Ti: 35% C-carbapenem: 15% p = 0.105 HR 2.6 p = 0.09 (Kaplan-Meier) **All-cause in-hospital mortality** C-Ti: 69% C-carbapenem: 50% p = 0.152	Pitt bacteremia score, SOFA score, platelet count, tigecycline use given tigecycline MIC >2(mg/L), Tigecycline use in pneumonic patient, CVC removal	Good
Kwon et al	Retrospective cohort study (observational)	2015 Republic of Korea	2011-2014	ICU	Adult patients who received IV CMS >72h for carbapenem-resistant *A.baumannii* pneumonia in the included time period	120	76 (62-80) and 78 (72-85)	Colistin	IV	a maximum of 30 days	airway	30-day mortality	absolute values	**30-day mortality** 33%	Age, dose per IBW, septic shock, length of stay	Good

Micha-lopoulos et al*	Prospec-tive obser-vational study	2007 Greece	2005-2006	ICU	All ICU patients who re-ceived nebulized col-istimethate sodium for VAP caused by MDR gram nega-tive bacteria	60	59.4 (±18.3)	Colistin	Inhala-tion	Until discharge or death	air-way	All-cause in-hos-pital mortal-ity Micro-biologi-cal and clinical success	abso-lute va-lues	**All-cause in-hospital mortality** 25% **Microbiolo-gical and cli-nical success** 83.3%	none	Poor

Abbreviations: No = number, incl = included patients with relevant infection, NR = not reported, H = hospital setting, ICU = Intensive care unit, XDR = extended drug resistant,VAP = ventilator associated pneumonia, cSSSI = complicated skin and skin structure infection, cIAI = complicated intra-abdominal infection, MDR = multidrug resistant, CMS = colistimethate sodium, C = colistin, Ti = tigecycline, Mi = Minocycline, Do = Doripenem, Fo = fosfomycin, R = rifampicin, Cp = Carbapenem, SB = sulbactam, AG = aminoglycosides, IV = intravenous, NG = nasogastric, BSI = bloodstream infection, NS = not significant, SAPS = Simplified Acute Physiology Score, APACHE II = Acute Physiology And Chronic Health Evaluation II, SOFA = sequential organ failure assessment, MIC = minimum inhibitory concentration, CVC = central venous catheter, IBW = ideal body weight

[A] = treatment based on growth inhibition in any well containing serum-achievable concentrations of drugs

[B] = treatment based on growth in all wells containing serum-achievable concentrations of drugs

[C]= ampicillin-sulbatam 18g/ 9g

[D] = ampicillin-sulbatam 24/12 g

[1] = colistin compared with colistin-carbapenem and colistin-sulbactam

[2] = colistin-carbapenem compared with colistin-sulbactam

*article including treatment and outcome for more than one bacteria therefore mentioned in more tables, but only included once in the study.

Greyscale = studies comparing treatment options

Table 3. Choice of treatment and outcomes for Stenotrophomonas maltophilia

Stenotrophomonas maltophilia																
Study characteristics																**Study quality**
Source	**Study type**	**Publication year and country of origin**	**Study period**	**Setting**	**Inclusion criteria**	**No. of patients (incl/all)**	**Mean age (years)**	**Antimicrobial treatment**	**Route**	**Follow up**	**Site of infection**	**Outcomes evaluated**	**Outcome measures**	**Results**	**Factors reported as being adjusted for**	**Quality assessment**
Mori et al	Systematic review	2014, Japan	up to 2013	H	Patients with hemorrhagic pneumonia caused by S.maltophilia	30	51.5	Co-trimoxazole- fluoroquinolones Co-trimoxazole Fluoroquinolones Broad spectrum antibiotics(- e.g. vancomycin or carbapenems)	NR	Until death or clinical success	airway	Clinical Success	Absolut values	**Clinical success** 0%	None	Poor
Falagas et al	Systematic review	2008, Taiwan	up to 2008	Various	Patient infected with S.maltophilia treated with an antibiotic regimen other than co-trimoxazole	49	52	Ciprofloxacin as monotherapy or in combination with other antibiotics. Ceftriaxone or ceftazidime as monotherapy or in combination with other antibiotics. Ticarcillin or ticarcillin/clavulate as monotherapy or in combination with other antibiotics	IV	Until death or clinical success	any	Clinical Success Mortality	Absolut values	**Clinical success** 66.7%-85% ciprofloxacin (combi or mono) 85% Ceftriaxone or ceftazidime (combi or mono) 50% Ticarcillin or ticarcillin/clavulate (combi or mono) 4/6 **Mortality** ciprofloxacin (combi or mono) 10% Ceftriaxone or	None	Poor

														ceftazidime (combi or mono) 16.7% Ticarcillin or ticarcillin/clavulate (combi or mono) 2/6		
Abbreviations: No = number, incl = included patients with relevant infection, NR = not reported, H = hospital setting, IV = intravenous																

Table 4. Choice of treatment and outcomes for ESBL-producing enterobacteriaceae

ESBL-producing *enterobacteriaceae*																
Study characteristics																**Study quality**
Reference	**Study type**	**Publication year and country of origin**	**Study period**	**Setting**	**Inclusion criteria**	**No. of patients (incl/all)**	**Mean age (years)**	**Antimicrobial treatment**	**Route**	**Follow-up**	**Site of infection**	**Outcomes evaluated**	**Outcome measures**	**Results**	**Factors reported as being adjusted for**	**Quality assessment**
Seo et al	Randomized, open-label comparison study	2017 Korea	2013-2015	H	Patients infected with a healthcare-associated urinary tract infection caused by ESBL *E. coli* that were susceptible to a randomized antibiotic in vitro	72	68.8 (±14.4) and 75.3 (±6.6) and 65.2 (±16.9)	Piperacillin-tazobactam or Cefepime or Ertapenem	NR	28-30 days	UTI	Clinical Success Microbiological success 28-day mortality	Absolute values	**Clinical success** PTZ: 93.9% Ertapenem: 97.0% Cefepime: 33.3% (p < 0.001) PTZ: 93.9% Ertapenem: 97.0% p = 0.50 **Microbiological success** PTZ: 97.0% Ertapenem: 97.0% Cefepime: 33.3% (p < 0.001) **28-day mortality** PTZ:6.1% Ertapenem 6.1%: Cefepime:33.3% (p = 0.108)	none	Poor
Yoon et al	Retrospective observational study	2017 Korea	2011-2013	H	Patients with acute pyelonephritis caused by Piperacillin/tazobactam susceptibility ESBL *e. coli* and treated with Piperacillin/tazobactam or ertapenem for 3 days or longer.	150	74 (60-79)	Piperacillin-tazobactam or Ertapenem	IV	A maximum of 33 days	UTI	In-hospital mortality Microbiological success	Absolute values	**In-hospital mortality** PTZ: 4.4% Ertapenem: 13.4% p = 0.059 **Microbiological success** PTZ: 95.6% Ertapenem: 95.1% p = 1.000	Length of hospital stay before APN onset, bacteremia, haematocrit <30%, septic shock, acute renal injury, prior receipt of immunosuppressive agents	Fair

Rattanaumpawan et al	Randomised controlled trial	2017 Thailand	2011-2014	H	Hospitalized patients 18 years or older with a documented ESBL-*enterobacteriaceae* infection who received group 2 carbapenems as empirical therapy.	66	64.8 (±19.6)	Group 2 carbapenems or group 1 carbapenems	IV	28 days	UTI Airways BS	Clinical success Microbiological success 28-day mortality	Absolute value	**Clinical success** De-escalation group[1]: 93.8% Non-de-escalation group: 79.4% p = 0.09 **Microbiological success** De-escalation group[1]: 100.0% Non-de-escalation group: 95.8% p = 0.36 **28-day mortality** De-escalation group[1]: 9.4 % Non-de-escalation group: 29.4% p = 0.05	Site of infection	Fair
Popejoy el al	Randomized, phase III clinical trial	2017 USA	NR	H	Patients with complicated urinary tract infection or complicated abdominal infection caused by ESBL-*enterobacteriaceae*	150	56 (18-87) and 49 (18-92)	**UTI** Ceftolozane- tazobactam or levofloxacin **cIAI** Ceftolozane- tazobactam+metronidazole or carbapenem	IV	cUTI: 5-9 days cIAI: 24-32 days:	UTI abdominal	Clinical success Microbiological success	Absolute value	**Clinical success** UTI Ceftolozane- tazobactam: 95.8% Levofloxacin: 82.6% p =0.011 cIAI Ceftolozane- tazobactam +metronidazole: 98.1% Carbapenem: 88.5% p > 0.05 **Microbiological success** Ceftolozane/tazobactam: 79.5% Other treatment (pooled): 62.5% p = 0.022	none	Fair
Gutiérrez et al	Retrospective cohort study (observational)	2016 Spain	2004-2013	H	Patients with clinically significant monomicrobial bloodstream infection due to ESBL-*enterobacteriaceae* who received	704	Empirical therapy cohort 66.5 (60.75-	ertapenem or other carbapenems	IV	30 days	BS	Clinical success 30-day mortality	OR HR	**Clinical success** *Empirical therapy group* Ertapenem: 90.6% Other carbapenems: 75.5%	Empirical therapy cohort: centre, age, gender, acquisition, type of	Fair

					monotherapy with ertapenem or another carbapenem (including imipenem, meropenem or doripenem)		75.25) and 66 (52-76) Targeted treatment cohort 71 (60-81) and 65 (52-77)							p = 0.06 Ertapenem: adjusted OR 1.87 (0.24–20.08; p=0.58) *Targeted therapy group* Ertapenem: 89.8% Other carbapenems: 82.6% p = 0.02 Ertapenem adjusted OR 1.04 95%CI 0.44–2.50; p =0.92 Propensity-matched cohorts: 95% CI 1.18 (0.43–3.29; p =0.74) **30-day mortality** *Empirical therapy group* Ertapenem: 3.1% Other carbapenems: 23.3% p = 0.01 *Targeted therapy group* Ertapenem: 9.3% Other carbapenems: 17.1% p = 0.01 Ertapenem HR 95% CI 0.93 (0.43–2.03; P=0.86) *Propensity-matched cohorts* HR 95%CI 1.05 (0.46–2.44; P=0.90)	hospital service, Pitt score, McCabe score, cancer, diabetes mellitus, chronic renal insufficiency, liver disease, cardiac disease, source presentation with severe sepsis/septic shock. Targeted therapy cohort: centre, age, gender, acquisition, type of hospital service, Pitt score, Charlson index, cancer, diabetes mellitus, chronic renal insufficiency, liver disease, cardiac disease, source, presentation with severe sepsis/septic shock, empirical therapy, appropriate empirical therapy	
Bassetti et al	prospective, open-label, non-	2007 Italy	2005-2006	ICU	Adult patients with signs of VAP symptoms within 7 days of mechanical ventilation	20	67 (±27)	Ertapenem	IV	A maximum of 21	airway	Clinical success Microbio-	Absolute values	**Clinical success** 80% **Microbiological**	none	Fair

	comparative pilot trial (observationel)				caused and radiographic evidence of pulmonary infiltrate. Infection caused by ESBL producing gram negative bacteria.					days		logical success		**success** 75%		
Goetheart et al	Retrospective cohort study (observational)	2006 Belgium	1994-2000	ICU	Critically ill patients infected with ESBL-*enterobacteriaceae* and treated with either cefepime or a carbapenem > 72 hour	43	59.7 (±19.7) and 64.2 (±13.6)	Cefepime or Carbapenem	IV	A maximum of 30 days	airway abdominal BS	Clinical success Microbiological success 30-day mortality rate	Absolute values	**Clinical success** Cefepime group: 62% Carbapenem group: 70% p = 0.59 **Microbiological success** Cefepime: 14% Carbapenem: 22% p = 0.76 **30-day mortality** Cefepime:33% Carbapenem: 26% p = 0.44	none	Fair
Kernéis et al	Retrospective observational study	2015 France	2012-2013	H	Patients infected with ESBL-*enterobacteriaceae* who were treated with cefoxitin	33	70 (23-93)	Cefoxitin	IV	14 days	UTI BS airway abdominal	Clinical success Microbiological success	Absolute values	**Clinical success** 3 day follow up: 90.9% 14 days follow up: 83.3% **Microbiological success** 70%	none (No significant differences in univariate and multivariate analysis)	Poor
Bin et al	Prospective observational study	2006 China	2002-2005	H	Patients with bacteremia due to ESBL-producing *E. coli* who had antimicrobial susceptibility test results of susceptible or intermediate to ceftazidime.	22	56.77	Ceftazidime or imipenem-cilastatin or cefoperazone-sulbactam	NR	30 days	BS	Clinical success Mortality	Absolute value	**Clinical success** ceftazidime: 85.7% imipenem-cilastatin: 87.5% cefoperazone-sulbactam: 71.4% p = 0.637	none	Fair
Solomkin et al	Randomized double-blind trial	2015, USA	2011-2013	H	Patients ≥18 years of age, with clinical evidence of cIAI. Operative or percutaneous drainage of an infectious focus was either planned or had been performed recently	58/806	50.8	ceftolozane-tazobactam+ metronidazole or meropenem	IV	24 hours, 24-32 days and 38-45 days	abdominal	Clinical success	Absolute value	**Clinical success** Ceftolozane-tazobactam+ metronidazole: 95.8% Meropenem: 88.5%	none	Good

					(within 24 hours), confirming the presence of cIAI.											
Tasbakan et al	Retrospective observational study	2012, Turkey	2006-2011	OCH	Patients >18 years with dysuria or problems with frequency or urgency in passing urine, >20 leukocytes/mm^3 in urine microscopy and culture proven ESBL-producing Nitrofurantoin sensitive *E. coli* in the urine (>10^5 CFU/mm^3)	75	54 (±17)	Nitrofurantoin	p.o.	A maximum of 31 days	UTI	Clinical success Microbiological success	Absolute value	**Clinical success** 69% **Microbiological success:** 68%	none	Fair
Ipekci et al	Retrospective observational study	2013, Taiwan	2013-2014	OC	Adult patients > 18 years, presenting with at least one of the typical symptoms; (dysuria, pollakiuria, urgency or supra-pubic pain), pyuria, a positive urine culture being for ESBL-producing *E. coli* or *K. pneumoniae* (resistant to nitrofurantoin, fosfomycin, quinolones and trimethoprim/sulfamethoxazole) and patients receiving intramuscular injections of 15 mg of amikacin per kg daily for 10 days.	36	59.12 (±18)	Amikacin	IM	Urine cultures at day 3, end of treatment, 7-10 days after treatment and 28-32 days after treatment	UTI	Clinical success Microbiological success	Absolute value	**Clinical success** 97.2% **Microbiological success** day 3: 91.7% end of treatment: 97.1% 7-10 days after treatment: 94.1%	noone	Fair
Lee et al (2013)	Retrospective observational study	2013, Taiwan	2002-2007	H	Patients with clinically significant monomicrobial bacteremia demonstrated via the isolation of ESBL producer alone	472	70	Cefepime or carbapenem	IV	a maximum of 30 days	BS	30-day crude mortality	OR	**30-day crude mortality** OR 7.1; 95% CI 2.5-20.3 p < 0.001	Urosepsis, Pitt bacteremia score ≥4, Rapidly fatal underlying dis-	Fair

					in blood cultures, compatible with sepsis syndrome and parenteral therapy with cefepime or a carbapenem for more than 48 hours until the end of antimicrobial therapy or death.										ease, Definitive therapy with cefepime	
Lo et al	Retrospective cohort study (observational)	2015, Taiwan	2008-2012	H	Adults (age >18 years) with ESBL-producing *E. coli* or *K. pneumoniae* (the isolation of an ESBL producer alone in blood culture(s)) bacteremia (symptoms compatible with sepsis syndrome) and parenteral therapy with a fluoroquinolone or carbapenem as definitive therapy.	299	70	fluoroquinolones or carbapenem	IV	a maximum of 30 days	BS	30-day mortality	Absolute value	**30-day mortality** FQ: 8.3% Carbapenem: 23.3% p=0.12 Matched group** 29.2% p=0.05 OR, 4.53; 95% CI, 0.98-21.00; p = 0.05	Hospital-onset bacteremia, pneumonia, urosepsis, rapid fatal underlying disease, Pitt bacteremia score ≥4	Fair
Lee et al (2011)	Retrospective observational study	2011, Taiwan	2002-2007	H	Adults (aged ≥18 years) with ESBL-producing *Escherichia coli* or *Klebsiella pneumoniae* bacteremia receiving a carbapenem (ertapenem, imipenem, or meropenem) for at least 72 h	244	66.2 (±17.4) and 67.8 (±14.7)	Imipenem-meropenem or ertapenem	NR	maximum of 30 days	BS	30-day crude mortality	Absolute value	**30-day crude mortality** Imipenem/meropenem: 17.6% Ertapenem: 16.4% p=1.0	none	Fair
Lee et al (2012)	Retrospective observational study	Taiwan, 2012	2002-2007	H	adults > 18 years with ESBL-producing *E. coli* and *K. pneumoniae* bacteremia who received carbapenem therapy more than 48 hours.	251	66.4 (±16.6) and 70.5 (±16.87)	appropriate therapy with carbapenems*** or inappropriate therapy with carbapenems	IV	until end of treatment or death	BS	Sepsis-related mortality	Absolute values	**Sepsis-related mortality** Appropriate therapy: 10.9% In-appropriate therapy: 38.1% p = 0.002	Severe sepsis, hospital-onset bacteremia, rapidly fatal underlying disease, pneumonia, appropriate antimicrobial therapy, ertapenem-non-susceptible isolates,	Fair
Collins et al	Retrospective cohort study (observational)	2012, USA	2005-2010	H	Adult (≥18 years old) patients with ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* BSI.	127/261	65.5 (±16.1)	Empirical therapy with group 1 carbapenem or Empirical therapy	NR	a maximum of 90 days	BS	In-hospital mortality 90-day mortality	OR	**In-hospital mortality** Group 1 carbapenem: 6.1% Group 2 carbapenem:18.3%	In-hospital mortality, 90-day mortality, functional status deterioration, median	Fair

								with group 2 carbapenem						OR (95% CI): 0.29 (0.08–1.0) p = 0.05 **90-day mortality** Empirical therapy: 12.2% Main therapy 33.3% OR (95% CI): 0.38 (0.14–0.99) P = 0.5	total LOS, median LOS from culture to discharge	
Carmeli et al*	Randomized phase III study	2016, Worldwide including 16 countries	2013-2014	H	Patients aged 18-90 years with ongoing symptoms of either complicated UTI or pyelonephritis or cIAI at the time of screening and an isolated causative Gram-negative ceftazidime-resistant pathogen could be included regardless of previous antibiotic therapy. Patients who had received previous antibacterial agents that were effective in vitro against the isolated pathogen (based on the known susceptibility profile of the organism) were required to have worsening of objective symptoms or signs of infection after 48 h or longer of therapy, or absence of improvement after 72 hours or longer of therapy.	21/333	64.3 (± 14.6) and 61.3 (±15.3) and 49.9 (±16.1) and 68.4 (±11.1)	CA or BAT	IV	TOC visit 7-10 days after last infusion of treatment therapy	UTI cIAI	Clinical success Microbiological success	absolut value	**Clinical success in UTI** CA: 91.6%% BAT: 93.9% **Microbiological success in UTI** CA: 81.67% BA: 64.39% **Clinical success in cIAI** CA: 88.88% BAT: 45.45%	none	Fair

Abbreviations: No = number, incl = included patients with relevant infection, NR = not reported, H = hospital setting, ICU = Intensive care unit, ESBL = extended spectrum beta-lactamase, BSI = bloodstream infection, VAP = Ventilator associated pneumonia, cIAI = complicated intra-abdominal infection, CFU = colony forming unit, IV = intravenous, p.o. = peroral, IM = intramuscular, UTI = urinary tract infection, BS = bloodstream, HA-UTI = healthcare-associated urinary tract infection, PTZ = Piperacillin-tazobactam, FQ = fluoroquinolone, APN = acute pyelonephritis, COPD = chronic obstructive pulmonary disease, LOS = length of stay,, LOS = length of hospital stay

*article including treatment and outcome for more than one bacteria therefore mentioned in more tables, but only included once in the study

**each patient receiving definitive fluoroquinolone therapy was matched to three patients with definitive carbapenem therapy with a similar propensity score

***treatment where the causative isolate was susceptible in vitro to the prescribed drug

[1]De-escalation therapy involves the initial use of empirical broad-spectrum antimicrobial therapy, which is then streamlined to more narrow-spectrum or targeted agents once culture and susceptibilities are available

Greyscale = studies comparing treatment options

Study 2 - Cross-sectional survey

1. Aim

To identify existing local and national guidelines and prescription habits in everyday clinical practice for MDR Gram-negative infection antibiotic therapy that are not captured by published guidelines and recommendations.

2. Methods

We conducteded a survey in six European countries, with different levels of resistance among important nosocomial pathogens: Denmark and the Netherlands (low MDR), the UK and France (medium MDR), and Romania and Greece (high MDR). In each of these six EU countries, through our consortium network, we have identified collaborators who are specialized in infections and microbial resistance. Our collaborators have offered help and advice in the local national surveys of clinicians and microbiologists in a range of reference hospitals about their therapeutic protocols and/or antibiotics prescribing patterns for treatment of MDR Gram-negative infections. Selected collaborators were a convenience sample, believed to be representative of the spectrum of the treating physicians in the underlying population. Most of the collaborators are from university hospitals, whereas few are from teaching/municipal hospitals, covering the large population susceptible for MDR bacteria due to centralization of treatment. Countries are selected due to different levels of MDR resistance among the important nosocomial pathogens: Denmark and the Netherlands (low MDR), the UK and France (medium MDR), and Romania and Greece (high MDR). We do not have precise information regarding the total number of hospitals working with MDR bacteria in each country, but have included several hospitals from each country.

A standard questionnaire and data collection methodology addressing existing clinical practice in antibiotic treatment of MDR Gram-negative bacteria was developed in Aarhus together with local cooperation partners and coordinators following a good practice in the conduct and reporting of survey research (87). Detailed instructions about purpose of survey, length of survey, confidentiality, anonymous presentation of the results, deadline for survey end, contact information, and how to fill in questionnaire was included in the questionnaire. A pilot test was performed at two hospital departments in the Netherlands in order to evaluate

the specific questions, format, question sequence and instructions prior to use in the main survey. The pilot test provided answers if each question measures what is intended to measure, if questions are interpreted in the same way by all participants, if questions are clear and understandable etc. The questionnaire was revised several times before final version was ready to be sent out for all participants.

Questionnaire was written in English language. The questionnaire was not translated into Greek, French and Romanian language after agreement with local cooperation partners and coordinators and participating clinicians/microbiologist. The questionnaire was based primarily multiple-choice items, but several open-ended items was also included. Multiple-choice questions are quicker and easier to answer and the answers are easier to analyze (88). Open-ended questions are important to allow participants to report more information than is possible with a discrete list of answers, and to freely elaborate on questions. Questions were grouped together and introduced by headings or short descriptive statements concerning treatment of each specific MDR Gram-negative bacteria. Both questions regarding localization, typical resistance, antibiotic treatment (empirical first and second treatment options), doses, length of treatment, way of administration (intravenous vs orally), monotherapy vs. combination therapy was included. Questions were asked about following MDR Gram-negative bacteria: *E. coli, P. aeruginosa, A. baumannii, enterobacteriaceae, and K. pneumonia.*
The survey was administered online using REDCap, a Web-based data management platform developed by a Vanderbilt University consortium (89) which is cost-saving, secure, easy to use and has high response rates. One reminder was sent out to non-responders after 3 weeks. Descriptive statistics including tables and figures were developed and pooled out from REDCap analyses system.
Based on survey, a REDCap report was produced summarizing current local treatment options for MDR Gram-negative bacteria and presented in short version in the result section. For full content of the questionnaire please see **Appendix 1**.

3. Results

Following data emerged from the survey.

General information

We have identified and invited to participate in survey clinicians/microbiologist from 17 hospitals in six countries, including three hospitals from Denmark, two from the Netherlands, three from the UK, three from France, five from Romania and one from Greece. Of these, 15 clinicians/microbiologist (88%) completed the survey, including at least one hospital from each of the six countries. In total, 30% of participated hospitals treat MDR Gram-negative bacteria almost daily, and 30% treat these infections less than once a week, whereas 15% and 24% of hospitals treat these infection less than once a month and less than once a year, respectively.

Clinicians/microbiologist have responded that the MDR Gram-negative infections they see, can manifest in different sites, including abscess (24%), bloodstream infections (35%), cardiac infections (14%), gastrointestinal infections (10%), musculoskeletal infections (24%), pulmonary infections (35%), soft tissue infections (21%), urinary tract infections (35%), wound or surgical site infections (21%).

Regarding the availability of guidelines for treatment of MDR Gram-negative infections at hospitals, 42% of clinicians/microbiologist answered that there is a guidelines at their hospitals, whereas 58% answered that there is no guidelines at their hospital. By guidelines, all clinicians/microbiologist stated that these are locally produces.

MDR E. coli

About 89% of responders treat MDR *E. coli* in their setting. The three most typical localizations for *E. coli* are urinary tract infection, pulmonary infection and bloodstream infection. *E.coli* bacteria are typically resistant to cephalosporins (62%), aminoglycosides (43%), quinolones (43%), and sulfonamides in combination with trimethoprim (33%).

Equally many responders answered that the empirical first choice treatment for suspected MDR E. coli infection is dependent and not dependent on localization of the infection. In 80% of cases, monotherapy is the empirical first choice treatment for suspected MDR *E. coli*, followed by combination of two drugs.

Following drugs are used as first choice monotherapy of suspected *E.coli:* meropenem (57%) and tobramycin (29%) in most cases, but also gentamicin, imipenem, amikacin and aztreonam in few cases. First choice treatment for bloodstream *E.coli* is colistin, for endocarditis is cefoxitin, for gastrointestinal infection is sulfamethoxazole in combination with trimethoprim, for

osteomyelitis is aztreonam, for soft tissue infection is ceftriaxone, and for urinary tract infection is ciprofloxacin (50%), amikacin, ceftriaxone, or meropenem. Would or surgical site infections are treated with colistin. All drugs are administrated intravenously. Duration of treatment is 5-7 days in 50% of cases, whereas 25% of cases are treated for 3-5 days or 7-10 days.

If *E.coli* was confirmed and susceptible for >2 drugs, 54% answered that they will treat infection with monotherapy and 46% answered that they will treat infection with combination of two drugs.

As second empirical choice of treatment for *E.coli* three drugs was used, including colistin (50%), tigecycline and gentamicin alone or in combination. For bloodstream *E.coli* infections, ertapenem was used as second choice, whereas for urinary tract infection *E. coli*, amikacin, cefepime and ertapenem were used as second choice. Duration of second choice treatment is 1-3 days in 25% of cases, 3-5 days in 50% cases and 5-7 days in 25% cases.

MDR ESBL-producing enterobacteriaceae

Only 22% of responders treat *enterobacteriaceae* in their setting. The two most typical localizations for *enterobacteriaceae* are urinary tract infection and soft tissue infections. *Enterobacteriaceae* are typically resistant to cephalosporins, aminoglycosides, and quinolones.

Typical first choice treatment is monotherapy with imipenem or meropenem, intravenously for 5-7 days. Second choice treatment is also monotherapy, but with colistin intravenously for 5-7 days.

MDR K. pneumoniae

About 60% of responders treat *K. pneum*onia in their setting. The three most typical localizations for K. pneumonia are urinary tract infection, pulmonary infection and bloodstream infection, but have been see also as wound or surgical site infections. *K. pneumonia* is typically (most commonly set) resistant to cephalosporins (83%), quinolones, monobactams and sulfonamides in combination with trimethoprim (50% cases for each drug), but also to aminoglycosides and carbapenems.

First choice treatment is in 83% of cases the same, irrespective of localization of the infection. As a first choice, meropenem monotherapy (89%) is most often used for 3-5 or 5-7 days. In case of urinary tract infection, imipenem is used. As a second choice treatment, monotherapy with colistin or tigecycline was preferable over combination of two drugs. However, second choice for bloodstream infection or urinary tract infections with *K. pneumonia* gentamicin or imipenem was preferred for 3-5 or 5-7 days.

MDR P. aeruginosa

About 62% of responders treat *P. auruginosa* in their setting. The two most typical localization are urinary tract infection and pulmonary infection. *P. auruginosa* is typically resistant to cephalosporins, carbapenems and aminoglycosides, but in some places also to sulfonamides in combination with trimethoprim and quinolones. Monotherapy is equally used as combination therapy, and treatment was in 66% of cases independent on localzation.

First choice empirical treatment for suspected *P. auruginosa* is colistin, followed by meropenem intravenously. Pulmonary infections with this bacteria is treated with amikacin is some cases, whereas urinary tract infections can be treated with imipenem. Typical treatment is 3-5 days, but most responders will extend treatment to 7-10 days if *P. auruginosa* infection is confirmed. Second choice treatment is often colistin or tigecycline for 3-5 days, but several participants answered that there is no available second choice treatment.

MDR A. baumannii

About 67% of responders treat *A. baumannii* in their setting. This infection can be seen in 9 different localization, but most typically as wound or surgical site infection, pulmonary infection and gastrointestinal infection.

A. baumannii is typically resistant to monobactams (46%), cephalosporins, sulfonamides in combination with trimethoprim, and carbapenems, but in some cases to aminoglycosides and quinolones too. Treatment is independent on localization in 70% of cases. First choice treatment is monotherapy in 60% of cases and combination of two drugs in 40% of cases.

As a first choice, monotherapy colistin is most often used for 7-10 days, followed by cefoxitin, meropenem and sulfamethoxazole in combination with trimethoprim. Pulmonary infection are often treated with moxifloxacin.

As a second choice treatment, monotherapy with colistin or tigecycline was preferable, but aztreonam, cefepime, cefotetan and ceftazidime are used as monotherapy up to 10 days. Both first and second choice treatment is administrated intravenously in most cases, but some patients are also treated per-orally and with other administration ways. About 25% of participants answered that there is no available second choice treatment for this bacteria.'

4. Conclusion

Response rate to survey was 88% (15/17 hospitals), including at least one hospital from countries with low, medium and high risk of MDR bacteria.

Less than half of the participants reported availability of local guidelines for treatment of MDR Gram-negative bacteria. Since participants were included in the process of production the local guidelines, the answers reflected the same one.

Participants have experience in treating *E. coli, P. aeruginosa, A. baumannii and K. pneumonia,* but were less experienced in treating *enterobacteriaceae.*

Each bacteria is typically resistant to at least three antibiotics and up to six different antibiotics.

Following drugs are used as first choice treatment of suspected MDR *E.coli:* monotherapy with **meropenem** and tobramycin in most cases, but also gentamicin, imipenem, amikacin and aztreonam in few cases. However, other antibiotics are used for specific localizations of *E. coli*.

As a second empirical choice of treatment for *E.coli* three drugs was used, including colistin, tigecycline and gentamicin, but other antibiotics can also be used in specific localizations.

Typical first choice treatment for ESBL-producing *enterobacteriaceae* is monotherapy with **imipenem** or **meropenem**. Second choice treatment is also monotherapy, but with colistin intravenously for 5-7 days.

As a first choice, **meropene**m is most often used for treatment of MDR *K. pneumonia*. As a second choice treatment, monotherapy with colistin or tigecycline was preferable over combination of two drugs. However, second choice for bloodstream infection or urinary tract infections with *K. pneumonia* gentamicin or imipenem was preferred.

First choice empirical treatment for suspected MDR *P. auruginosa* is **meropenem**, colistin or imipenem intravenously up to 10 days. Second choice treatment is colistin or tigecycline 3-5 days.

As a first choice treatment for *A. baumannii*, monotherapy **colistin** is most often used for 7-10 days. As a second choice treatment, monotherapy with colistin or tigecycline was preferable, but aztreonam, cefepime, cefotetan and ceftazidime are used as monotherapy up to 10 days.

Our survey confirm that large variation in the resistant, first and second choice treatment, as well in the duration of treatment for MDR Gram-negative bacteria. Meropenem, colistin and imipenem seem to be included as first choice treatment for almost all studied MDR Gram-negative bacteria.

Study 3 - Cohort study

1. Aim

To conduct a cohort study in Denmark (population = 5.6 million persons) based on existing routinely and prospectively collected data from population-based medical and administrative registries. The Danish National Health Service provides tax-supported healthcare to all Danish residents, guaranteeing universal access to primary and secondary medical care.
The aim of cohort study was to describe characteristics of patients who sustained MDR Gram-negative bacteria causing urinary tract infection and examine adverse outcomes such as complications and death related to specific MDR bacterial infection.

2. Methods

2.1. Data sources

We used data from the from the unique microbiological Laboratory Information System database of the North Denmark Region, linked with the Danish National Patient Registry (DNPR), the Danish Civil Registration System (DCRS), and the Danish National Health Service Prescription Database (DNHSPD).

The Department of Clinical Microbiology, Aalborg University Hospital, provides bacteriological services for hospitals and general practitioners from the entire study/catchment area (90). The department's Laboratory Information System database (based on a microbiological database system ADBakt, Autonik AB; Ramsta, Sköldinge, Sweden) holds information on all microbiological specimens submitted to the department including information on date of culture, bacterial species, and antibiotic susceptibility.
The DNPR (91) includes information of all hospitalized patients since 1977 and outpatient hospital contact since 1995. The register contains information about the date of admission, discharge, type of admissions, diagnosis codes and surgical procedures. From 1977 to 1993 diagnosis codes were coded with reference to the *International Classification of Diseases* [*Eight Revision* (ICD-8) and from 1994 onward diagnoses have been coded with reference to *Tenth Revision* (ICD-10).
The DCRS, established in 1968, assigns a unique ten-digit personal identification number, encoding age, sex and date of birth, to all Danish residents at birth or upon immigration, enabling

individual-level linkage across all registries (92). The DCRS also tracks' migrations, residence, and vital status.

The DNHSPD (93) has maintained information on all prescriptions for reimbursed drugs dispensed by community pharmacies in Denmark since 2004, recorded according to the Anatomical Therapeutic Chemical classification system (ATC codes). Additional variables in the DNHSPD include drug name, package identifier (permitting identification of brand, quantity, and drug formulation), date of refill, code identifying the prescribing physician, and code identifying the dispensing pharmacy.

2.2. Study period

Data sources were available for analysis for the period 2007-2012. **We have applied for microbiology data up to 2016, but have not received these data before EMA report deadline.**

2.3. Study population

MDR exposed cohort (ESBL cohort): All MDR E.coli urinary tract infection recorded in the North Denmark region during the period 2004-2013 were ascertained from the microbiological Laboratory Information System. However, we included all persons with a first diagnosis of ESBL E.coli urinary tract infection from 2007 to 2012 due to exclusion of cases with diagnoses of any MDR bacterial Gram-negative infection from 2004 to 2006, ensuring 3 years lookback period. Lookback period of 3 years was chosen in orden to ensure that include cases are the-incident MDR bacteria cases rather than reccurent cases. We only choose patients > 15 years of age since distribution, risk factors and treatment of MDR bacteria is slightly different in adults and children. In

Comparison cohort (non-ESBL cohort): To examine the impact of MDR infection per se, we created a cohort of patients with first non- ESBL E.coli urinary tract infection registered in the same microbiological Laboratory Information System and residing in the Region of Northern Denmark.

General population comparison cohort (population cohort): We identify 10 persons for each member of ESBL cohort from the general population using the DCRS who were alive at the MDR ESBL E.coli urinary tract infection index date and never were tested positive for any MDR bacteria within one week of the index date for MDR ESBL E.coli case.

Index date was defined as date of first ESBL urinary tract infection in exposed cohort and as date of first non-EXBL urinary tract infection in comparison cohort.

2.4. Outcomes and covariates

We ascertain morbidity (any hospitalization up to 365 days of index date, short-term mortality (0-30 days post index date), and subsequent long-term mortality (31-365 days post index date) comparing persons included in the three cohorts.

We ascertained antibiotic therapy given before and after the index date for the MDR and non-MDR infected patient cohorts using the DNHSPD, to examine treatment outcomes associated with given antibiotic therapies, and any effect modification of the MDR/non-MDR – outcome associations by therapy.

All covariates are listed and described in **Appendix 2**.

Figure 6. Flow diagram - Identification of ESBL, non-ESBL and population cohorts.

2.5. Statistical analyses

All patients were followed from the index date until death, hospitalization, emigration or November 30, 2013, whichever came first. We calculated mortality rates per 1000 person years. We used Poisson regression analyses to calculate mortality rate ratios with 95% confidence intervals comparing the MDR exposure cohort with the two comparison cohorts. We adjusted for age, gender, and preexisting comorbidity. We used the DNPR to obtain a complete medical history for all persons in the study cohorts from 1977 until the index date. As a measure of comorbidity, we will compute the Charlson Comorbidity Index (CCI) score (94) for each person at the index date and define three comorbidity levels: a score of 0 (low), given to patients with no previous record of conditions included in the CCI; a score of 1-2 (medium); and a score of 3 or more (high). Due to low sample size we were not able to study potential differences in the association between exposure to MDR bacteria and mortality risk in subgroups of patients stratifying on gender, age groups, and calendar year of Index date. Due to large variety in antibiotic therapy and combination possibilities (resulting in small sample sizes), we were not able to examine the association between type of antibiotic therapy given and clinical outcomes by MDR Gram-negative bacteria status.

3. Results

We identified 393 patients with ESBL E. coli urinary tract infection, 12,998 patients with non-ESBL E. coli urinary tract infection, and 3930 population comparisons during 2007-2012.
Only 15 E.coli patients were excluded due to age less than 15 years.
Patients with ESBL E. coli urinary tract infection were older (median age 68 years) than non-ESBL (63 years) and population cohort (48 years), and had more severe comorbidity burden (CCI score of more than 0 was 58%, vs. 40% and 22% of comparisons cohorts, respectively). ESBL had higher prevalence of all specific pre-existing morbidity included in the CCI. Number of hospital inpatient admissions within 365 days before index date was higher in ESBL patients (48%) compared with non-ESBL patients (27%) and population cohort (12%). ESBL patients had received any antibiotics within 31-365 days before the index date in 78% of cases, compared with 56% and 29% of cases in non-ESBL patients and population cohort, respectively (Table 5). Patients with ESBL were also more likely to have redeemed a prescription for both broad and narrow spectrum antibiotics and penicillin, as well as mecillinam, sulfamethizole, macrolides, and nitrofurantoin. Almost half of the ESBL patients (46%) had surgery due to any

reason compared with 33% and 24% of non-ESBL patients and population cohort cases, respectively (Table 5).

The risk of being inpatient hospitalized within 30 days was 15% in ESBL E. coli urinary tract infection patients, versus 6% in non-ESBL patients and 1% in general population comparison cohort (Figure 3), corresponding to adjusted rate ratios of 2.0 (95% CI 1.5-2.6) and 7.3 (95% CI 4.6-11.5), respectively. In contrast, adjusted one-year mortality was not increased in ESBL versus non-ESBL E. coli urinary tract infection patients (adjusted rate ratio 1.1, 95% CI 0.8-1.6), yet was 2.1-fold (95% CI 1.3-3.5) higher than in the general population cohort. Number of deaths within 30 days was too low to provide meaningful rate ratio estimates (Table 6A and 6B).

Use of antibiotics within 30 days of index date is presented in Table 7A. Broad spectrum antibiotics were used within 30 days of index date in 32% and 20% of ESBL and non-ESBL patients, respectively, followed by use of narrow spectrum antibiotics (21% and 16%). Two most common used antibiotics in ESBL and non-ESBL group before infection were Mecillinam (23% and 17%) and Sulfamethizole (8% and 8%). Combination treatment was applied in about 10% of ESBL infections, f.eks. broad /narrow spectrum antibiotics combination was used in 8% and 4% of ESBL and non-ESBL patients, narrow spectrum antibiotics/mecillinam combination was used in 5% and 3% of ESBL and non-ESBL patients. Further combinations were used within 30 days of index date including mecillinam combined with sulfamethizole, trimethoprim, mactrolides or nitrofurantoin, and sulfamethizole combined with trimethoprim, macrolides or nitrofurantoin.

Use of antibiotics from index date to seven days after index date is presented in Table 7B. Broad spectrum antibiotics were used up to seven days of index date in 28% and 50% of ESBL and non-ESBL patients, respectively, followed by use of narrow spectrum antibiotics (23% and 26%). Two most common used antibiotics in ESBL and non-ESBL group within seven days of infection were Mecillinam (26% and 46%) and Sulfamethizole (10% and 19%). Combinations of antibiotics used after the index date were similar to that before the index date.

Table 8 shows the association between different antibiotics (groups or single type) used +/-30 days of the index date and mortality/hospitalization during 31-365 days. No clear association between any of the antibiotic therapy and mortality/hospitalization was observed.

Thus, the likelihood of having received community antibiotics was increased in ESBL vs. non-ESBL patients 30 days before the urinary tract infection, whereas the likelihood of community antibiotic therapy appeared to be decreased in ESBL vs non-ESBL patients 7 days after urinary tract infection diagnosis.

4. Discussion

In this large population based cohort study we observed that ESBL urinary tract infection patients were at 2-fold and 7-fold increased risk of being hospitalized within 30 days of infection diagnosis compared with non-ESBL urinary tract infection patients and general population cohort, respectively. However, one year mortality was similar in ESBL versus non-ESBL patients, but 2-fold higher compared with general population cohort. Both ESBL and non-ESBL patients were treated with different antibiotics (monotherapy or combination therapy) before and after infection diagnosis. Variety of antibiotic treatment resulted in small sample sizes enabling us to study the association between treatment and mortality/hospitalization.

Strengths and limitations

Strengths of our study include its population based design in a setting with unfettered access to health care, avoiding referral and diagnostic biases. The use of updated data on prescriptions and hospitalization history minimized selection bias, and provided a long study period and a large sample size compared with previous studies. Data on ESBL and non-ESBL patients were collected from the same data source, minimizing selection bias.

Limitations of our study include the lack of data on antibiotics dispensing at hospitals. Since only a small proportion of the total antibiotic use in Denmark is dispensed in hospitals (in 2012 the volume of antibiotics was 2 defined daily dose per 1000 inhabitants per day (DID) in hospitals compared with 17 DID in primary care), the reported antibiotic use within seven days of the index date might be underestimated. Given that ESBL patients were older and more comorbid than non-ESBL patients, resulting in longer hospital stay, the underestimation is likely to differ among ESBL and non-ESBL patients, leading to differential misclassification. Our study was conducted in a setting with low antibiotic use and low prevalence of ESBL E.coli compare with many other countries, which may hinder the extrapolation of our results to other settings. For example, cephalosporins are not used in Danish primary care.

Our data on similar mortality in ESBL compared with non-ESBL urinary tract infected patients within a one year of diagnosis are not in accordance with one previous study from UK (95). This study included all sites of infection, but most common was urine (68%). Among these, odds ratio for death was 6.33 (CI): 1.99-20.09). The higher mortality in ESBL urinary tract infection patients in previous studies was suggested to be partly be explained by patient's high age and comorbidity, and thereby greater vulnerability. We have adjusted for age and comorbidity. Since ESBL patients are more often hospitalized in our study, which will increase their risk to be treated for infection and improve and optimize their vulnerability, and subsequently might be possible explanation for similar mortality in ESBL versus non-ESBL patients we have observed. In general, bacteremia cased by ESBL producing Enterobacteriaceae is associated with higher mortality and delay in effective therapy (96, 97). However, not all previous studies have observed increased mortality in ESBL patients, but longer inpatient stay and more frequent admission to the intensive care unit (98, 99). Adjustment for ineffective empirical therapy leads to a reduction in relative mortality, indicating that higher mortality in ESBL patients is likely to be mediated through this phenomenon. Likewise, adjustment for detailed comorbidity may lead to a reduction in relative mortality.

Conclusion

Compared with non-ESBL urinary tract infection patients, ESBL patients have higher risk of being hospitalized up to one year of infection, whereas the mortality was similar in these two groups.

Study 3 – Cohort study, Tables 5-8

Table 5. Characteristics of the study population

	ESBL UTI		non-ESBL UTI*		Population cohort	
	N	%	N	%	N	%
Total	393	100	12,998	100	3,930	100
Year of index date						
2007	8	2.0	1,694	13.0	80	2.0
2008	34	8.7	1,786	13.7	340	8.7
2009	57	14.5	2,115	16.3	570	14.5
2010	56	14.2	2,318	17.8	560	14.2
2011	104	26.5	2,534	19.5	1,040	26.5
2012	134	34.1	2,551	19.6	1,340	34.1
Male Sex	96	24.4	2,283	17.6	1,967	50.1
Age, years						
15 - 50	98	24.9	4,449	34.2	2,121	54.0
51 - 50	49	12.5	1,570	12.1	670	17.0
61 - 70	71	18.1	2,332	17.9	609	15.5
71 - 80	82	20.9	2,314	17.8	345	8.8
81+	93	23.7	2,333	17.9	185	4.7
Charlson comorbidity index score						
0	166	42.2	7,785	59.9	3,052	77.7
1-2	139	35.4	3,720	28.6	717	18.2
3+	88	22.4	1,493	11.5	161	4.1
Coexisting comorbidities						
Myocardial infarction	24	6.1	505	3.9	78	2.0
Congestive heart failure	25	6.4	458	3.5	58	1.5
Peripheral vascular disease	23	5.9	538	4.1	102	2.6
Cerebrovascular disease	41	10.4	1,249	9.6	145	3.7
Dementia	17	4.3	349	2.7	18	0.5
Chronic pulmonary disease	57	14.5	1,172	9.0	242	6.2
Connective tissue disease	28	7.1	539	4.1	85	2.2
Ulcer disease	33	8.4	690	5.3	80	2.0
Mild liver disease	8	2.0	124	1.0	17	0.4
Diabetes I and II	43	10.9	864	6.6	101	2.6
Hemiplegia	7	1.8	69	0.5	9	0.2
Moderate to severe renal disease	37	9.4	352	2.7	41	1.0
Diabetes with end organ	21	5.3	419	3.2	52	1.3

	ESBL UTI		non-ESBL UTI*		Population cohort	
	N	%	N	%	N	%
Any tumor	69	17.6	1,459	11.2	192	4.9
Leukemia	1	0.3	42	0.3	6	0.2
Lymphoma	3	0.8	60	0.5	15	0.4
Moderate to severe liver disease	1	0.3	19	0.1	7	0.2
Metastatic solid tumor	8	2.0	131	1.0	19	0.5
AIDS	1	0.3	2	0.0	0	0.0
Any antibiotics within 31-365 days before the index date	307	78.1	7,277	56.0	1,128	28.7
- Broad spectrum antibiotics	227	57.8	4,004	30.8	343	8.7
- Narrow spectrum antibiotics	245	62.3	5,704	43.9	967	24.6
- Broad spectrum penicillin	87	22.1	1,323	10.2	200	5.1
- Narrow spectrum penicillin	99	25.2	3,038	23.4	667	17.0
- Mecillinam	199	50.6	3,271	25.2	167	4.2
- Sulfamethizole	92	23.4	2,009	15.5	89	2.3
- Macrolides	69	17.6	1,219	9.4	273	6.9
- Nitrofurantoin	55	14.0	596	4.6	22	0.6
Any surgical procedure	181	46.1	4,246	32.7	923	23.5
- Genitourinary tract	56	14.2	1,508	11.6	312	7.9
- Gastrointestinal tract	44	11.2	964	7.4	178	4.5
- Orthopedic	23	5.9	279	2.1	52	1.3
- Thorax	77	19.6	1,497	11.5	322	8.2
- Skin and soft tissue	47	12.0	939	7.2	217	5.5
Number of hospital inpatient admissions within 365 days before index date						
0	204	51.9	9,521	73.2	3,463	88.1
1-2	127	32.3	2,907	22.4	424	10.8
3+	62	15.8	570	4.4	43	1.1

*UTI- urinary tract infection

Table 6A. Risk of mortality and hospitalization in ESBL and non-ESBL UTI patients*

Outcome	Exposure	N at risk	No of out-comes	Person-years	Crude rate per 1,000 person-years (95% CI)	Crude rate ratio (95% CI)	Adjusted rate ratio (95% CI)
Mortality 0-30 days	ESBL UTI	393	2	32.2	62.0 (7.5 - 224.1)	0.6 (0.1 - 2.2)	0.4 (0.1 - 1.4)
	non-ESBL UTI	12,998	119	1,062.9	112.0 (92.8 - 134.0)		
Mortality 31-365 days	ESBL UTI	391	33	340.9	96.8 (66.6 - 136.0)	1.6 (1.2 - 2.3)	1.1 (0.8 - 1.6)
	non-ESBL UTI	12,877	676	11416.0	59.2 (54.8 - 63.9)		
Hospitalization 0-30 days	ESBL UTI	390	58	29.1	1995.3 (1515.1 - 2579.4)	2.5 (1.9 - 3.2)	2.0 (1.5 - 2.6)
	non-ESBL UTI	12,899	824	1,017.4	809.9 (755.5 - 867.2)		
Hospitalization 31-365 days	ESBL UTI	332	114	234.7	485.7 (400.6 - 583.5)	1.4 (1.2 - 1.7)	1.3 (1.1 - 1.6)
	non-ESBL UTI	12,009	3,118	9,206.2	338.7 (326.9 - 350.8)		

*UTI- urinary tract infection

Table 6B. Risk of mortality and hospitalization in ESBL UTI patients and population co-hort*

Outcome	Exposure	N at risk	No of out-comes	Person-years	Crude rate per 1,000 person-years (95% CI)	Crude rate ratio (95% CI)	Adjusted rate ratio (95% CI)
Mortality 0-30 days	ESBL UTI	393	2	32.2	62.0 (7.5 - 224.1)	5.0 (0.9 - 27.3)	1.1 (. - .)
	Population cohort	3,930	4	322.3	12.4 (3.4 - 31.8)		
Mortality 31-365 days	ESBL UTI	391	33	340.9	96.8 (66.6 - 136.0)	7.8 (5.0 - 12.3)	2.1 (1.3 - 3.5)
	Population cohort	3,921	44	3,555.8	12.4 (9.0 - 16.6)		
Hospitalization 0-30 days	ESBL UTI	390	58	29.1	1995.3 (1515.1 - 2579.4)	12.5 (8.5 - 18.3)	7.3 (4.6 - 11.5)
	Population cohort	3,917	51	319.2	159.8 (118.9 - 210.0)		
Hospitalization 31-365 days	ESBL UTI	332	114	234.7	485.7 (400.6 - 583.5)	3.8 (3.0 - 4.7)	2.1 (1.6 - 2.7)
	Population cohort	3,858	426	3,299.0	129.1 (117.2 - 142.0)		

*UTI- urinary tract infection

Table 7A. Use of antibiotics within 30 days before the index date

	ESBL UTI		non-ESBL UTI*		Population cohort	
	N	%	N	%	N	%
Total	393	100	12,998	100	3,930	100
Any antibiotics within 30 days before the index date (index date not included)	178	45.3	4,248	32.7	164	4.2
- Broad spectrum antibiotics	125	31.8	2,610	20.1	46	1.2
- Narrow spectrum antibiotics	83	21.1	2,108	16.2	133	3.4
- Broad spectrum penicillin	37	9.4	511	3.9	25	0.6
- Narrow spectrum penicillin	20	5.1	628	4.8	84	2.1
- Mecillinam	91	23.2	2,203	16.9	22	0.6
- Sulfamethizole	33	8.4	993	7.6	11	0.3
- Trimethoprim	20	5.1	250	1.9	6	0.2
- Macrolides	6	1.5	183	1.4	33	0.8
- Nitrofurantoin	14	3.6	209	1.6	2	0.1
Combinations						
- Broad and narrow spectrum antibiotics	30	7.6	470	3.6	15	0.4
- Broad spectrum antibiotics and narrow spectrum penicillin	8	2.0	123	0.9	7	0.2
- Broad spectrum antibiotics and sulfamthizole	9	2.3	192	1.5	2	0.1
- Broad spectrum antibiotics and trimethoprim	5	1.3	74	0.6	1	0.0
- Broad spectrum antibiotics and macrolides	2	0.5	44	0.3	5	0.1
- Broad spectrum antibiotics and nitrofurantoin	10	2.5	74	0.6	0	0.0
- Narrow spectrum antibiotics and broad spectrum penicillin	12	3.1	105	0.8	11	0.3
- Narrow spectrum antibiotics and mecillinam	20	5.1	385	3.0	4	0.1
- Broad and narrow spectrum penicillin	2	0.5	28	0.2	5	0.1
- Broad spectrum penicillin and mecillinam	5	1.3	109	0.8	3	0.1
- Broad spectrum penicillin and sulfamethizole	5	1.3	35	0.3	1	0.0
- Broad spectrum penicillin and trimethoprim	2	0.5	18	0.1	0	0.0
- Broad spectrum penicillin and macrolides	1	0.3	20	0.2	5	0.1
- Broad spectrum penicillin and nitrofurantoin	3	0.8	15	0.1	0	0.0
- Narrow spectrum penicillin and mecillinam	6	1.5	99	0.8	2	0.1
- Narrow spectrum penicillin and trimethoprim	0	0.0	13	0.1	0	0.0
- Narrow spectrum penicillin and macrolides	1	0.3	23	0.2	3	0.1
- Narrow spectrum penicillin nitrofurantoin	0	0.0	8	0.1	0	0.0
- Mecillinam and sulfamethizole	6	1.5	163	1.3	1	0.0
- Mecillinam and trimethoprim	3	0.8	63	0.5	1	0.0
- Mecillinam and macrolides	1	0.3	27	0.2	0	0.0
- Mecillinam and nitrofurantoin	7	1.8	60	0.5	0	0.0

	ESBL UTI		non-ESBL UTI*		Population cohort	
	N	%	N	%	N	%
- Sulfamethizole and trimethoprim	2	0.5	30	0.2	0	0.0
- Sulfamethizole and macrolides	1	0.3	9	0.1	0	0.0
- Sulfamethizole and nitrofurantoin	1	0.3	20	0.2	0	0.0
- Trimethoprim and macrolides	0	0.0	6	0.0	0	0.0
- Trimethoprim and nitrofurantoin	0	0.0	16	0.1	0	0.0
- Macrolides and nitrofurantoin	2	0.5	5	0.0	0	0.0

*UTI- urinary tract infection

Table 7B. Use of antibiotics from index date to 7 days after index date

	ESBL UTI		non-ESBL UTI*		Population cohort	
	N	%	N	%	N	%
Total	393	100	12,998	100	3,930	100
Any antibiotics from index date (included) to 7 days after index date (not included)	183	46.6	9,378	72.1	42	1.1
- Broad spectrum antibiotics	110	28.0	6,469	49.8	13	0.3
- Narrow spectrum antibiotics	90	22.9	3,381	26.0	31	0.8
- Broad spectrum penicillin	9	2.3	510	3.9	3	0.1
- Narrow spectrum penicillin	7	1.8	90	0.7	21	0.5
- Mecillinam	101	25.7	6,025	46.4	10	0.3
- Sulfamethizole	41	10.4	2,433	18.7	2	0.1
- Trimethoprim	14	3.6	482	3.7	4	0.1
- Macrolides	2	0.5	58	0.4	5	0.1
- Nitrofurantoin	30	7.6	392	3.0	0	0.0
Combinations						
- Broad and narrow spectrum antibiotics	17	4.3	472	3.6	2	0.1
- Broad spectrum antibiotics and narrow spectrum penicillin	3	0.8	36	0.3	0	0.0
- Broad spectrum antibiotics and sulfamthizole	6	1.5	264	2.0	1	0.0
- Broad spectrum antibiotics and trimethoprim	2	0.5	85	0.7	1	0.0
- Broad spectrum antibiotics and macrolides	0	0.0	23	0.2	0	0.0
- Broad spectrum antibiotics and nitrofurantoin	7	1.8	68	0.5	0	0.0
- Narrow spectrum antibiotics and broad spectrum penicillin	2	0.5	62	0.5	0	0.0
- Narrow spectrum antibiotics and mecillinam	15	3.8	415	3.2	2	0.1
- Broad and narrow spectrum penicillin	0	0.0	2	0.0	0	0.0
- Broad spectrum penicillin and mecillinam	1	0.3	77	0.6	0	0.0
- Broad spectrum penicillin and sulfamethizole	0	0.0	34	0.3	0	0.0
- Broad spectrum penicillin and trimethoprim	0	0.0	10	0.1	0	0.0
- Broad spectrum penicillin and macrolides	0	0.0	1	0.0	0	0.0

	ESBL UTI		non-ESBL UTI*		Population cohort	
	N	%	N	%	N	%
- Broad spectrum penicillin and nitrofurantoin	2	0.5	15	0.1	0	0.0
- Narrow spectrum penicillin and mecillinam	3	0.8	34	0.3	0	0.0
- Narrow spectrum penicillin and trimethoprim	0	0.0	3	0.0	0	0.0
- Narrow spectrum penicillin and macrolides	0	0.0	1	0.0	1	0.0
- Narrow spectrum penicillin nitrofurantoin	0	0.0	1	0.0	0	0.0
- Mecillinam and sulfamethizole	6	1.5	233	1.8	1	0.0
- Mecillinam and trimethoprim	2	0.5	76	0.6	1	0.0
- Mecillinam and macrolides	0	0.0	22	0.2	0	0.0
- Mecillinam and nitrofurantoin	5	1.3	54	0.4	0	0.0
- Sulfamethizole and trimethoprim	0	0.0	21	0.2	0	0.0
- Sulfamethizole and macrolides	0	0.0	7	0.1	0	0.0
- Sulfamethizole and nitrofurantoin	3	0.8	22	0.2	0	0.0
- Trimethoprim and macrolides	0	0.0	0	0.0	0	0.0
- Trimethoprim and nitrofurantoin	1	0.3	8	0.1	0	0.0
- Macrolides and nitrofurantoin	0	0.0	2	0.0	0	0.0

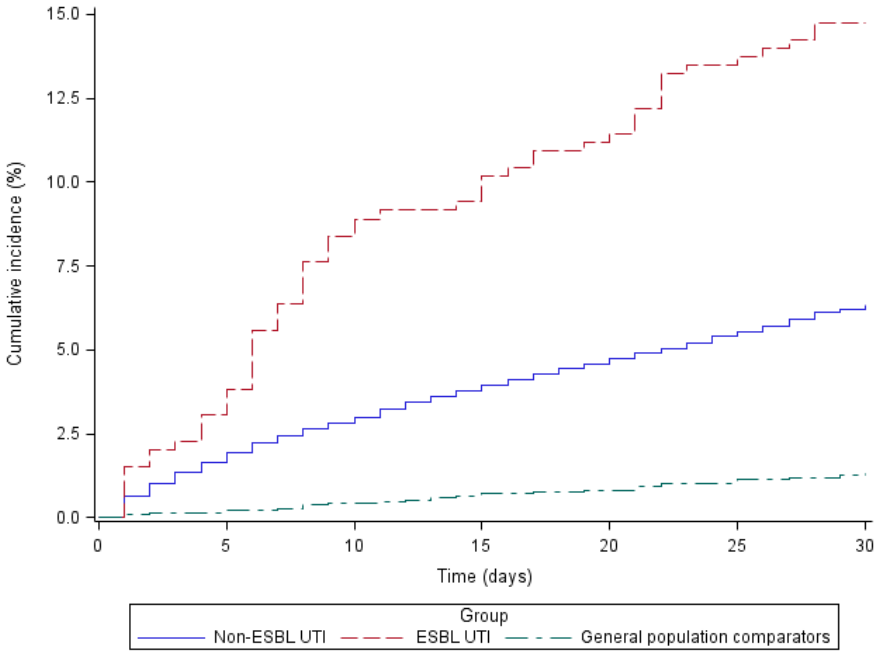
*UTI- urinary tract infection

Table 8. Use of antibiotics from 30 days before to 30 days after index date in ESBL and non-ESBL patients

Outcome	Type of antibiotics	Exposure	N at risk	No of out-comes	Person-years	Crude rate per 1,000 person-years (95% CI)	Crude rate ratio (95% CI)	Adjusted rate ratio (95% CI)
Mortality	No antibiotics	ESBL UTI	65	4	57.4	69.7 (19.0 - 178.5)	1.1 (0.4 - 3.0)	0.7 (0.2 - 2.0)
		non-ESBL UTI	1,316	74	1,160.8	63.7 (50.1 - 80.0)		
	Any antibiotics	ESBL UTI	326	29	283.5	102.3 (68.5 - 146.9)	1.7 (1.2 - 2.5)	1.2 (0.8 - 1.7)
		non-ESBL UTI	11,561	602	10255.1	58.7 (54.1 - 63.6)		
	Broad spectrum antibiotics	ESBL UTI	225	23	194.3	118.4 (75.0 - 177.6)	1.8 (1.2 - 2.8)	1.3 (0.9 - 2.0)
		non-ESBL UTI	8,744	495	7,733.9	64.0 (58.5 - 69.9)		
	Narrow spectrum antibiotics	ESBL UTI	206	21	178.4	117.7 (72.9 - 180.0)	1.9 (1.2 - 2.9)	1.3 (0.8 - 2.0)
		non-ESBL UTI	5,915	333	5,235.9	63.6 (57.0 - 70.8)		
	Broad spectrum penicillin	ESBL UTI	52	6	45.5	131.7 (48.3 - 286.7)	1.5 (0.7 - 3.4)	1.0 (0.5 - 2.2)
		non-ESBL UTI	1,277	96	1,113.8	86.2 (69.8 - 105.3)		
	Narrow spectrum penicillin	ESBL UTI	39	7	32.0	218.6 (87.9 - 450.5)	2.2 (1.0 - 4.9)	1.4 (0.6 - 3.1)
		non-ESBL UTI	883	75	769.2	97.5 (76.7 - 122.2)		
	Mecillinam	ESBL UTI	193	19	166.9	113.9 (68.6 - 177.8)	1.8 (1.1 - 2.9)	1.4 (0.9 - 2.2)
		non-ESBL UTI	8,166	453	7,227.1	62.7 (57.0 - 68.7)		
	Sulfamethizole	ESBL UTI	85	6	75.1	79.9 (29.3 - 174.0)	1.5 (0.7 - 3.4)	0.9 (0.4 - 2.0)
		non-ESBL UTI	3,820	178	3,402.2	52.3 (44.9 - 60.6)		
	Trimethoprim	ESBL UTI	52	9	43.3	207.7 (95.0 - 394.4)	2.1 (1.0 - 4.0)	1.6 (0.8 - 3.2)
		non-ESBL UTI	1,104	97	961.2	100.9 (81.8 - 123.1)		
	Macrolides	ESBL UTI	15	1	13.0	76.7 (1.9 - 427.1)	0.8 (0.1 - 6.1)	0.8 (. - .)
		non-ESBL UTI	333	27	287.4	94.0 (61.9 - 136.7)		
	Nitrofurantoin	ESBL UTI	80	6	71.0	84.5 (31.0 - 183.8)	1.1 (0.5 - 2.6)	1.2 (0.5 - 2.9)
		non-ESBL UTI	821	55	722.3	76.1 (57.4 - 99.1)		
Hospitalization	No antibiotics	ESBL UTI	54	21	36.8	571.0 (353.4 - 872.8)	1.4 (0.9 - 2.2)	1.5 (0.9 - 2.3)
		non-ESBL UTI	1,205	358	891.6	401.5 (361.0 - 445.3)		
	Any antibiotics	ESBL UTI	278	93	197.9	469.8 (379.2 - 575.6)	1.4 (1.1 - 1.8)	1.3 (1.0 - 1.6)
		non-ESBL UTI	10,804	2,760	8,314.6	331.9 (319.7 - 344.6)		
	Broad spectrum antibiotics	ESBL UTI	192	68	132.1	514.6 (399.6 - 652.4)	1.4 (1.1 - 1.8)	1.3 (1.0 - 1.7)
		non-ESBL UTI	8,124	2,207	6,159.6	358.3 (343.5 - 373.6)		
	Narrow spectrum antibiotics	ESBL UTI	176	53	128.6	412.2 (308.8 - 539.1)	1.3 (1.0 - 1.8)	1.2 (0.9 - 1.6)
		non-ESBL UTI	5,520	1,334	4,296.2	310.5 (294.1 - 327.6)		
	Broad spectrum penicillin	ESBL UTI	45	18	30.7	586.3 (347.5 - 926.6)	1.2 (0.7 - 2.0)	1.2 (0.8 - 1.9)
		non-ESBL UTI	1,125	384	792.8	484.3 (437.1 - 535.3)		
	Narrow spectrum penicillin	ESBL UTI	31	13	19.9	654.5 (348.5 - 1119.2)	1.8 (1.0 - 3.1)	1.4 (0.7 - 2.5)

Outcome	Type of antibiotics	Exposure	N at risk	No of out-comes	Person-years	Crude rate per 1,000 person-years (95% CI)	Crude rate ratio (95% CI)	Adjusted rate ratio (95% CI)
		non-ESBL UTI	779	217	583.0	372.2 (324.3 - 425.2)		
	Mecillinam	ESBL UTI	166	60	113.5	528.5 (403.3 - 680.3)	1.5 (1.2 - 2.0)	1.4 (1.1 - 1.9)
		non-ESBL UTI	7,601	2,021	5,795.8	348.7 (333.7 - 364.2)		
	Sulfamethizole	ESBL UTI	72	20	54.4	367.7 (224.6 - 567.9)	1.4 (0.9 - 2.1)	1.2 (0.7 - 1.9)
		non-ESBL UTI	3,641	786	2,892.9	271.7 (253.0 - 291.4)		
	Trimethoprim	ESBL UTI	44	13	32.9	394.9 (210.2 - 675.2)	0.9 (0.5 - 1.5)	0.8 (0.5 - 1.5)
		non-ESBL UTI	1,008	321	732.9	438.0 (391.4 - 488.6)		
	Macrolides	ESBL UTI	12	1	10.2	98.1 (2.5 - 546.6)	0.3 (0.0 - 1.8)	0.3 (0.0 - 2.3)
		non-ESBL UTI	293	82	223.9	366.3 (291.3 - 454.7)		
	Nitrofurantoin	ESBL UTI	73	21	53.0	396.1 (245.2 - 605.5)	1.0 (0.6 - 1.5)	1.0 (0.6 - 1.6)
		non-ESBL UTI	749	229	555.3	412.4 (360.7 - 469.4)		

Figure 7: 30 days incidence of hospitalization after ESBL vs. non-ESBL UTI and population cohort



Reference list

1. Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. P T. 2015;40(4):277-83.
2. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2012;18(3):268-81.
3. Nikaido H. Multidrug resistance in bacteria. Annu Rev Biochem. 2009;78:119-46.
4. Prevention CfDCa. Antibiotic resistance threats in the United States, 2013. 2013 4/23/2013.
5. Antimicrobial resistance surveillance in Europe 2014. Annual report of the European Antimicrobial
Resistance Surveillance Network (EARS-Net). 2014.
6. WHO. Antimicrobial resistance: global report on surveillance 2014. 2014.
7. Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. P & T : a peer-reviewed journal for formulary management. 2015;40(4):277-83.
8. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis. 2009;48(1):1-12.
9. Khan SN, Khan AU. Breaking the Spell: Combating Multidrug Resistant 'Superbugs'. Front Microbiol. 2016;7:174.
10. Taneja N, Kaur H. Insights into Newer Antimicrobial Agents Against Gram-negative Bacteria. Microbiology insights. 2016;9:9-19.
11. Rossolini GM, Arena F, Pecile P, Pollini S. Update on the antibiotic resistance crisis. Current opinion in pharmacology. 2014;18:56-60.
12. Munoz-Price LS, Poirel L, Bonomo RA, Schwaber MJ, Daikos GL, Cormican M, et al. Clinical epidemiology of the global expansion of Klebsiella pneumoniae carbapenemases. Lancet Infect Dis. 2013;13(9):785-96.
13. Control ECfDPa. Antimicrobial resistance surveillance in Europe 2014. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockhold: ECDC.; 2015 11/1/2015.
14. Ramphal R, Ambrose PG. Extended-spectrum beta-lactamases and clinical outcomes: current data. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2006;42 Suppl 4:S164-72.
15. Chopra T, Marchaim D, Veltman J, Johnson P, Zhao JJ, Tansek R, et al. Impact of cefepime therapy on mortality among patients with bloodstream infections caused by extended-spectrum-beta-lactamase-producing Klebsiella pneumoniae and Escherichia coli. Antimicrobial agents and chemotherapy. 2012;56(7):3936-42.
16. Lee CS, Doi Y. Therapy of Infections due to Carbapenem-Resistant Gram-Negative Pathogens. Infection & chemotherapy. 2014;46(3):149-64.
17. Dijkshoorn L, Nemec A, Seifert H. An increasing threat in hospitals: multidrug-resistant Acinetobacter baumannii. Nature reviews Microbiology. 2007;5(12):939-51.
18. Li J, Nation RL, Turnidge JD, Milne RW, Coulthard K, Rayner CR, et al. Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections. The Lancet Infectious diseases. 2006;6(9):589-601.
19. Fournier PE, Richet H. The epidemiology and control of Acinetobacter baumannii in health care facilities. Clin Infect Dis. 2006;42(5):692-9.
20. Prevention CfDCa. Acinetobacter baumannii infections among patients at military medical facilities treating injured U.S. service members, 2002-2004. JAMA. 2004;292(24):2964-6.

21. Brooke JS. Stenotrophomonas maltophilia: an emerging global opportunistic pathogen. Clinical microbiology reviews. 2012;25(1):2-41.
22. Giske CG, Monnet DL, Cars O, Carmeli Y. Clinical and economic impact of common multidrug-resistant gram-negative bacilli. Antimicrob Agents Chemother. 2008;52(3):813-21.
23. Zowawi HM, Harris PN, Roberts MJ, Tambyah PA, Schembri MA, Pezzani MD, et al. The emerging threat of multidrug-resistant Gram-negative bacteria in urology. Nat Rev Urol. 2015;12(10):570-84.
24. Control ECfDPa. European Centre for Disease Prevention and Control. Summary of the latest data on antibiotic resistance in the European Union. Stockholm: ECDC; 2016. 2016.
25. Gandra S, Barter DM, Laxminarayan R. Economic burden of antibiotic resistance: how much do we really know? Clin Microbiol Infect. 2014;20(10):973-80.
26. David N. Gilbert HFC, George M. Epiopoulos, Michael S. Saag, Andrew T. Pavia, Douglas Black, David O Freedman, Kami Kim, Brian S. Schwartz. The Sanford guide. To Antimicrobial therapy 2017. 47th ed2017.
27. Zowawi HM, Harris PN, Roberts MJ, Tambyah PA, Schembri MA, Pezzani MD, et al. The emerging threat of multidrug-resistant Gram-negative bacteria in urology. Nature reviews Urology. 2015;12(10):570-84.
28. Harris P, Paterson D, Rogers B. Facing the challenge of multidrug-resistant gram-negative bacilli in Australia. The Medical journal of Australia. 2015;202(5):243-7.
29. Tacconelli E, Cataldo MA, Dancer SJ, De Angelis G, Falcone M, Frank U, et al. ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2014;20 Suppl 1:1-55.
30. Giamarellou H, Poulakou G. Multidrug-resistant Gram-negative infections: what are the treatment options? Drugs. 2009;69(14):1879-901.
31. Izadpanah M, Khalili H. Antibiotic regimens for treatment of infections due to multidrug-resistant Gram-negative pathogens: An evidence-based literature review. J Res Pharm Pract. 2015;4(3):105-14.
32. Livermore DM, Warner M, Mushtaq S, Doumith M, Zhang J, Woodford N. What remains against carbapenem-resistant Enterobacteriaceae? Evaluation of chloramphenicol, ciprofloxacin, colistin, fosfomycin, minocycline, nitrofurantoin, temocillin and tigecycline. Int J Antimicrob Agents. 2011;37(5):415-9.
33. Poulikakos P, Tansarli GS, Falagas ME. Combination antibiotic treatment versus monotherapy for multidrug-resistant, extensively drug-resistant, and pandrug-resistant Acinetobacter infections: a systematic review. Eur J Clin Microbiol Infect Dis. 2014;33(10):1675-85.
34. Rafailidis PI, Falagas ME. Options for treating carbapenem-resistant Enterobacteriaceae. Curr Opin Infect Dis. 2014;27(6):479-83.
35. Taneja N, Kaur H. Insights into Newer Antimicrobial Agents Against Gram-negative Bacteria. Microbiol Insights. 2016;9:9-19.
36. Tamma PD, Cosgrove SE, Maragakis LL. Combination therapy for treatment of infections with gram-negative bacteria. Clinical microbiology reviews. 2012;25(3):450-70.
37. Fitzpatrick JM, Biswas JS, Edgeworth JD, Islam J, Jenkins N, Judge R, et al. Gram-negative bacteraemia; a multi-centre prospective evaluation of empiric antibiotic therapy and outcome in English acute hospitals. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2016;22(3):244-51.
38. Anneline Seegert CSJ, Sarah Melissa Nørgaard, Josefine Aalestrup, Abeda Samadi. Anti-microbial resistance: Choice of therapeutic interventions and outcomes for the treatment of infections caused by MDR Gram-negative pathogens –a systematic review. 2017.
39. The National Heart LaBI. Study Quality Assessment Tools: U.S. Department of Health & Human Services; [Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.

40. Sorli L, Luque S, Segura C, Campillo N, Montero M, Esteve E, et al. Impact of colistin plasma levels on the clinical outcome of patients with infections caused by extremely drug-resistant Pseudomonas aeruginosa. BMC infectious diseases. 2017;17(1):11.
41. Montero M, Horcajada JP, Sorli L, Alvarez-Lerma F, Grau S, Riu M, et al. Effectiveness and safety of colistin for the treatment of multidrug-resistant Pseudomonas aeruginosa infections. Infection. 2009;37(5):461-5.
42. Wright A, Hawkins CH, Anggard EE, Harper DR. A controlled clinical trial of a therapeutic bacteriophage preparation in chronic otitis due to antibiotic-resistant Pseudomonas aeruginosa; a preliminary report of efficacy. Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery. 2009;34(4):349-57.
43. Carmeli Y, Armstrong J, Laud PJ, Newell P, Stone G, Wardman A, et al. Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and Pseudomonas aeruginosa complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study. The Lancet Infectious diseases. 2016;16(6):661-73.
44. Alvarez-Marin R, Lopez-Rojas R, Marquez JA, Gomez MJ, Molina J, Cisneros JM, et al. Colistin Dosage without Loading Dose Is Efficacious when Treating Carbapenem-Resistant Acinetobacter baumannii Ventilator-Associated Pneumonia Caused by Strains with High Susceptibility to Colistin. PLoS One. 2016;11(12):e0168468.
45. Bremmer DN, Bauer KA, Pouch SM, Thomas K, Smith D, Goff DA, et al. Correlation of Checkerboard Synergy Testing with Time-Kill Analysis and Clinical Outcomes of Extensively Drug-Resistant Acinetobacter baumannii Respiratory Infections. Antimicrobial agents and chemotherapy. 2016;60(11):6892-5.
46. Yilmaz GR, Guven T, Guner R, Kocak Tufan Z, Izdes S, Tasyaran MA, et al. Colistin alone or combined with sulbactam or carbapenem against A. baumannii in ventilator-associated pneumonia. Journal of infection in developing countries. 2015;9(5):476-85.
47. Lopez-Cortes LE, Cisneros JM, Fernandez-Cuenca F, Bou G, Tomas M, Garnacho-Montero J, et al. Monotherapy versus combination therapy for sepsis due to multidrug-resistant Acinetobacter baumannii: analysis of a multicentre prospective cohort. The Journal of antimicrobial chemotherapy. 2014;69(11):3119-26.
48. Batirel A, Balkan, II, Karabay O, Agalar C, Akalin S, Alici O, et al. Comparison of colistin-carbapenem, colistin-sulbactam, and colistin plus other antibacterial agents for the treatment of extremely drug-resistant Acinetobacter baumannii bloodstream infections. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology. 2014;33(8):1311-22.
49. Vasilev K, Reshedko G, Orasan R, Sanchez M, Teras J, Babinchak T, et al. A Phase 3, open-label, non-comparative study of tigecycline in the treatment of patients with selected serious infections due to resistant Gram-negative organisms including Enterobacter species, Acinetobacter baumannii and Klebsiella pneumoniae. The Journal of antimicrobial chemotherapy. 2008;62 Suppl 1:i29-40.
50. Saballs M, Pujol M, Tubau F, Pena C, Montero A, Dominguez MA, et al. Rifampicin/imipenem combination in the treatment of carbapenem-resistant Acinetobacter baumannii infections. The Journal of antimicrobial chemotherapy. 2006;58(3):697-700.
51. Ye JJ, Lin HS, Kuo AJ, Leu HS, Chiang PC, Huang CT, et al. The clinical implication and prognostic predictors of tigecycline treatment for pneumonia involving multidrug-resistant Acinetobacter baumannii. J Infect. 2011;63(5):351-61.
52. Kim WY, Moon JY, Huh JW, Choi SH, Lim CM, Koh Y, et al. Comparable Efficacy of Tigecycline versus Colistin Therapy for Multidrug-Resistant and Extensively Drug-Resistant Acinetobacter baumannii Pneumonia in Critically Ill Patients. PLoS One. 2016;11(3):e0150642.
53. Goff DA, Bauer KA, Mangino JE. Bad bugs need old drugs: a stewardship program's evaluation of minocycline for multidrug-resistant Acinetobacter baumannii infections. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2014;59 Suppl 6:S381-7.

54. Cheng A, Chuang YC, Sun HY, Sheng WH, Yang CJ, Liao CH, et al. Excess Mortality Associated With Colistin-Tigecycline Compared With Colistin-Carbapenem Combination Therapy for Extensively Drug-Resistant Acinetobacter baumannii Bacteremia: A Multicenter Prospective Observational Study. Critical care medicine. 2015;43(6):1194-204.
55. Kwon KH, Oh JY, Yoon YS, Jeong YJ, Kim KS, Shin SJ, et al. Colistin treatment in carbapenem-resistant Acinetobacter baumannii pneumonia patients: Incidence of nephrotoxicity and outcomes. International journal of antimicrobial agents. 2015;45(6):605-9.
56. Michalopoulos A, Fotakis D, Virtzili S, Vletsas C, Raftopoulou S, Mastora Z, et al. Aerosolized colistin as adjunctive treatment of ventilator-associated pneumonia due to multidrug-resistant Gram-negative bacteria: a prospective study. Respiratory medicine. 2008;102(3):407-12.
57. Motaouakkil S, Charra B, Hachimi A, Nejmi H, Benslama A, Elmdaghri N, et al. Colistin and rifampicin in the treatment of nosocomial infections from multiresistant Acinetobacter baumannii. J Infect. 2006;53(4):274-8.
58. Sirijatuphat R, Thamlikitkul V. Preliminary study of colistin versus colistin plus fosfomycin for treatment of carbapenem-resistant Acinetobacter baumannii infections. Antimicrobial agents and chemotherapy. 2014;58(9):5598-601.
59. Aydemir H, Akduman D, Piskin N, Comert F, Horuz E, Terzi A, et al. Colistin vs. the combination of colistin and rifampicin for the treatment of carbapenem-resistant Acinetobacter baumannii ventilator-associated pneumonia. Epidemiology and infection. 2013;141(6):1214-22.
60. Betrosian AP, Frantzeskaki F, Xanthaki A, Douzinas EE. Efficacy and safety of high-dose ampicillin/sulbactam vs. colistin as monotherapy for the treatment of multidrug resistant Acinetobacter baumannii ventilator-associated pneumonia. J Infect. 2008;56(6):432-6.
61. Betrosian AP, Frantzeskaki F, Xanthaki A, Georgiadis G. High-dose ampicillin-sulbactam as an alternative treatment of late-onset VAP from multidrug-resistant Acinetobacter baumannii. Scandinavian journal of infectious diseases. 2007;39(1):38-43.
62. Durante-Mangoni E, Signoriello G, Andini R, Mattei A, De Cristoforo M, Murino P, et al. Colistin and rifampicin compared with colistin alone for the treatment of serious infections due to extensively drug-resistant Acinetobacter baumannii: a multicenter, randomized clinical trial. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2013;57(3):349-58.
63. Mori M, Tsunemine H, Imada K, Ito K, Kodaka T, Takahashi T. Life-threatening hemorrhagic pneumonia caused by Stenotrophomonas maltophilia in the treatment of hematologic diseases. Annals of hematology. 2014;93(6):901-11.
64. Falagas ME, Valkimadi PE, Huang YT, Matthaiou DK, Hsueh PR. Therapeutic options for Stenotrophomonas maltophilia infections beyond co-trimoxazole: a systematic review. The Journal of antimicrobial chemotherapy. 2008;62(5):889-94.
65. Yoon YK, Kim JH, Sohn JW, Yang KS, Kim MJ. Role of piperacillin/tazobactam as a carbapenem-sparing antibiotic for treatment of acute pyelonephritis due to extended-spectrum beta-lactamase-producing Escherichia coli. International journal of antimicrobial agents. 2017;49(4):410-5.
66. Gutierrez-Gutierrez B, Bonomo RA, Carmeli Y, Paterson DL, Almirante B, Martinez-Martinez L, et al. Ertapenem for the treatment of bloodstream infections due to ESBL-producing Enterobacteriaceae: a multinational pre-registered cohort study. The Journal of antimicrobial chemotherapy. 2016;71(6):1672-80.
67. Bassetti M, Righi E, Fasce R, Molinari MP, Rosso R, Di Biagio A, et al. Efficacy of ertapenem in the treatment of early ventilator-associated pneumonia caused by extended-spectrum beta-lactamase-producing organisms in an intensive care unit. The Journal of antimicrobial chemotherapy. 2007;60(2):433-5.
68. Goethaert K, Van Looveren M, Lammens C, Jansens H, Baraniak A, Gniadkowski M, et al. High-dose cefepime as an alternative treatment for infections caused by TEM-24 ESBL-producing Enterobacter aerogenes in severely-ill patients. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2006;12(1):56-62.

69. Kerneis S, Valade S, Geri G, Compain F, Lavollay M, Rostane H, et al. Cefoxitin as a carbapenem-sparing antibiotic for infections caused by extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae. Infectious diseases (London, England). 2015;47(11):789-95.
70. Bin C, Hui W, Renyuan Z, Yongzhong N, Xiuli X, Yingchun X, et al. Outcome of cephalosporin treatment of bacteremia due to CTX-M-type extended-spectrum beta-lactamase-producing Escherichia coli. Diagnostic microbiology and infectious disease. 2006;56(4):351-7.
71. Tasbakan MI, Pullukcu H, Sipahi OR, Yamazhan T, Ulusoy S. Nitrofurantoin in the treatment of extended-spectrum beta-lactamase-producing Escherichia coli-related lower urinary tract infection. International journal of antimicrobial agents. 2012;40(6):554-6.
72. Ipekci T, Seyman D, Berk H, Celik O. Clinical and bacteriological efficacy of amikacin in the treatment of lower urinary tract infection caused by extended-spectrum beta-lactamase-producing Escherichia coli or Klebsiella pneumoniae. Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy. 2014;20(12):762-7.
73. Lee NY, Huang WH, Tsui KC, Hsueh PR, Ko WC. Carbapenem therapy for bacteremia due to extended-spectrum beta-lactamase-producing Escherichia coli or Klebsiella pneumoniae. Diagnostic microbiology and infectious disease. 2011;70(1):150-3.
74. Lee NY, Lee CC, Huang WH, Tsui KC, Hsueh PR, Ko WC. Carbapenem therapy for bacteremia due to extended-spectrum-beta-lactamase-producing Escherichia coli or Klebsiella pneumoniae: implications of ertapenem susceptibility. Antimicrobial agents and chemotherapy. 2012;56(6):2888-93.
75. Lee NY, Lee CC, Huang WH, Tsui KC, Hsueh PR, Ko WC. Cefepime therapy for monomicrobial bacteremia caused by cefepime-susceptible extended-spectrum beta-lactamase-producing Enterobacteriaceae: MIC matters. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2013;56(4):488-95.
76. Lo CL, Lee CC, Li CW, Li MC, Hsueh PR, Lee NY, et al. Fluoroquinolone therapy for bloodstream infections caused by extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae. Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi. 2015;50(3):355-61.
77. Collins VL, Marchaim D, Pogue JM, Moshos J, Bheemreddy S, Sunkara B, et al. Efficacy of ertapenem for treatment of bloodstream infections caused by extended-spectrum-beta-lactamase-producing Enterobacteriaceae. Antimicrobial agents and chemotherapy. 2012;56(4):2173-7.
78. Seo YB, Lee J, Kim YK, Lee SS, Lee JA, Kim HY, et al. Randomized controlled trial of piperacillin-tazobactam, cefepime and ertapenem for the treatment of urinary tract infection caused by extended-spectrum beta-lactamase-producing Escherichia coli. BMC infectious diseases. 2017;17(1):404.
79. Rattanaumpawan P, Werarak P, Jitmuang A, Kiratisin P, Thamlikitkul V. Efficacy and safety of de-escalation therapy to ertapenem for treatment of infections caused by extended-spectrum-beta-lactamase-producing Enterobacteriaceae: an open-label randomized controlled trial. BMC infectious diseases. 2017;17(1):183.
80. Popejoy MW, Paterson DL, Cloutier D, Huntington JA, Miller B, Bliss CA, et al. Efficacy of ceftolozane/tazobactam against urinary tract and intra-abdominal infections caused by ESBL-producing Escherichia coli and Klebsiella pneumoniae: a pooled analysis of Phase 3 clinical trials. The Journal of antimicrobial chemotherapy. 2017;72(1):268-72.
81. Solomkin J, Hershberger E, Miller B, Popejoy M, Friedland I, Steenbergen J, et al. Ceftolozane/Tazobactam Plus Metronidazole for Complicated Intra-abdominal Infections in an Era of Multidrug Resistance: Results From a Randomized, Double-Blind, Phase 3 Trial (ASPECT-cIAI). Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2015;60(10):1462-71.
82. Bassetti M, Repetto E, Righi E, Boni S, Diverio M, Molinari MP, et al. Colistin and rifampicin in the treatment of multidrug-resistant Acinetobacter baumannii infections. The Journal of antimicrobial chemotherapy. 2008;61(2):417-20.

83. Park SH, Choi SM, Chang YK, Lee DG, Cho SY, Lee HJ, et al. The efficacy of non-carbapenem antibiotics for the treatment of community-onset acute pyelonephritis due to extended-spectrum beta-lactamase-producing Escherichia coli. The Journal of antimicrobial chemotherapy. 2014;69(10):2848-56.
84. Falagas ME, Rafailidis PI, Kasiakou SK, Hatzopoulou P, Michalopoulos A. Effectiveness and nephrotoxicity of colistin monotherapy vs. colistin-meropenem combination therapy for multidrug-resistant Gram-negative bacterial infections. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2006;12(12):1227-30.
85. Poulikakos P, Tansarli GS, Falagas ME. Combination antibiotic treatment versus monotherapy for multidrug-resistant, extensively drug-resistant, and pandrug-resistant Acinetobacter infections: a systematic review. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology. 2014;33(10):1675-85.
86. Izadpanah M, Khalili H. Antibiotic regimens for treatment of infections due to multidrug-resistant Gram-negative pathogens: An evidence-based literature review. Journal of research in pharmacy practice. 2015;4(3):105-14.
87. Kelley K, Clark B, Brown V, Sitzia J. Good practice in the conduct and reporting of survey research. Int J Qual Health Care. 2003;15(3):261-6.
88. Hulley SB, Cummings SR, Browner, W.S., Grady DG, Newman TB. Designing Clinical Research. Fourth edition: Lippincott Williams & Wilkins, a Wolters Kluwer business, Philadelphia, USA; 2013 2013.
89. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-81.
90. Schonheyder HC, Sogaard M. Existing data sources for clinical epidemiology: The North Denmark Bacteremia Research Database. Clin Epidemiol. 2010;2:171-8.
91. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015;7:449-90.
92. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol. 2014;29(8):541-9.
93. Johannesdottir SA, Horvath-Puho E, Ehrenstein V, Schmidt M, Pedersen L, Sorensen HT. Existing data sources for clinical epidemiology: The Danish National Database of Reimbursed Prescriptions. Clin Epidemiol. 2012;4:303-13.
94. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.
95. Melzer M, Petersen I. Mortality following bacteraemic infection caused by extended spectrum beta-lactamase (ESBL) producing E. coli compared to non-ESBL producing E. coli. J Infect. 2007;55(3):254-9.
96. Rottier WC, Ammerlaan HS, Bonten MJ. Effects of confounders and intermediates on the association of bacteraemia caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae and patient outcome: a meta-analysis. The Journal of antimicrobial chemotherapy. 2012;67(6):1311-20.
97. Schwaber MJ, Carmeli Y. Mortality and delay in effective therapy associated with extended-spectrum beta-lactamase production in Enterobacteriaceae bacteraemia: a systematic review and meta-analysis. The Journal of antimicrobial chemotherapy. 2007;60(5):913-20.
98. Denis B, Lafaurie M, Donay JL, Fontaine JP, Oksenhendler E, Raffoux E, et al. Prevalence, risk factors, and impact on clinical outcome of extended-spectrum beta-lactamase-producing Escherichia coli bacteraemia: a five-year study. Int J Infect Dis. 2015;39:1-6.
99. Osthoff M, McGuinness SL, Wagen AZ, Eisen DP. Urinary tract infections due to extended-spectrum beta-lactamase-producing Gram-negative bacteria: identification of risk

factors and outcome predictors in an Australian tertiary referral hospital. Int J Infect Dis. 2015;34:79-83.

Appendix 1. Survey form for cross-sectional study 2

Attached separately as pdf fil

Appendix 2. Covariates included in the cohort study 3

variable	Data Source	Sub-category	Codes	Notes
Covariates				
Sex	Civil Registration System			
Age	Civil Registration System			
Acid_related_drugs	Danish National Health Service Prescription Database		A02	Look 365 back from Index date
Antibiotic any	Danish National Health Service Prescription Database	Categorized in the following categories: 31-365 days 0-365 days	J01	Look 365 back from Index date
Broad-spectrum		Categorized in the following categories: 0-365 days 31-365 days	J01AA J01CA J01CR J01DB J01DC J01DD J01DH J01EE J01GB J01MA J01XB	Look 365 back from Index date
Narrow-spectrum		Categorized in the following categories: 0-365 31-365 days	J01BA J01CE J01CF J01DE J01DF J01EA J01EB J01FA J01FF J01XA J01XC J01XD J01XE J01XX	Look 365 back from Index date
Penicillin_broad		Categorized in the following categories: 0-365 31-365 days	J01CA except J01CA08, J01CR	Look 365 back from Index date

Penicillin_narrow		Categorized in the following categories: 0-365 31-365 days	J01CE J01CF	Look 365 back from Index date
Mecillinam		Categorized in the following categories: 0-365 days 31-365 days	J01CA08	Look 365 back from Index date
Sulfamethizole		Categorized in the following categories: 0-365 days 31-365 days	J01EB02	Look 365 back from Index date
Trimethoprim		Categorized in the following categories: 0-365 days 31-365 days	J01EA01	Look 365 back from Index date
Macrolides		Categorized in the following categories: 0-365 days 31-365 days	J01F	Look 365 back from Index date
				Look 365 back from Index date
				Look 365 back from Index date
Nitrofurantoin		Categorized in the following categories: 0-365 days 31-365 days	J01XE01	Look 365 back from Index date

Prior_admission	Danish National Patient Registry			hospital inpatient admissions within 1 year prior to the index date. We would like to know the number of prior admissions.
Surgical_procedures	Danish National Patient Registry	Genitourinary tract	KK KL KM	Look one year prior index date
		Gastrointestinal tract	KJ	
		Thorax	KF KG	
		Orthopedic	KN	
		Skin and soft tissue	KQ	
Surgical_procedures_overall	Danish National Patient Registry	All of the above except for skin and soft tissue		Look one year prior index date
Civilstatus	Civil Registration System	Married	G	At index date
		Never married	U P	
		Divorced or widowed	F E O	
		Unknown		
Citizenship	Civil Registration System	Northern EU (DK, N, SE, Finland, Faroe Islands) vs other		
Hospitalization history	Danish National Patient Registry		C_diag C_diagtype C_tildiag D_inddto D_uddto	Look back to 1977
Each of the 19 individual Charlson diseases				Look back to 1977
Charlson Comorbidity Index score				Look back to 1977
Outcome				

Vital status	Civil Registration System	0-30 and 31-365 days		d.d.
Any readmission	Danish National Patient Registry	0-30 and 31-365 days		After index date
Acute readmission	Danish National Patient Registry	0-30 and 31-365 days		After index date
Length of hospital stay	Danish National Patient Registry	For current UTI		Index date (inddto - uddto)
ICU therapy	Danish National Patient Registry		Procedurekoden ”NABE” eller ”NABB” i SKS_UBEfilen i LPR. Datoen for proceduren (d_odto) er indlæggelsesdato.	
Renal diseases	Danish National Patient Registry		N00 N01 N03 N04 N05 I12 I13 I151 I151 N11 N14 N15 N16 Q611 Q612 Q613 Q614 E102 E112 E142 N083 N18 N19 N26 N27 N07 N08	After index date
Antibiotic any and specific use for current UTI	Danish National Health Service Prescription Database			Look 30 days after index date Evt. From -30 to +30 days
Exposure				
ESBL cohort Non-ESBL cohort Background population cohort	Microbiology data and Civil Registration System			