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Treatment in Infections by *Enterobacterales* Producing Extended Spectrum Betalactamase. Systematic Review

Tratamiento en infecciones por Enterobacterales que producen betalactamasa de espectro extendido. Revisión Sistemática

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Abstract

Extended spectrum beta-lactamases producing Enterobacterales have become pandemic worldwide representing a major public health threat due to poor outcomes and high mortality associated with infections by these bacteria, consequently it is essential to conduct a systematic review to document the antibiotic combination used to fight infections, in order to categorize and sort the most widely used treatments and determine the most effective ones. The electronic search was conducted since June 2020 until August 2020. The databases used were PubMed, Virtual Health Library, ScienceDirect and the Cochrane library; the following Medical Subject Headings (MESH) were used: "*Enterobacterales*", "infection", "beta-lactamase", "beta-lactamase inhibitors", "therapeutics", "*Enterobacteriaceae*/enzymology". The electronic search resulted in 1.526 articles meeting the general criteria, 1.493 articles were excluded; only 35 articles met all the inclusion criteria. there is basically no tangible difference between treatment with beta-lactam antibiotics (either combinations or carbapenem), fluoroquinolones, tetracyclines and Fosfomycin in patients without any pre-existing antibiotic resistance. It is required developing antibiotics, with the understanding that the microorganism will respond to them and resistance will develop (an evolutionary fact). Therefore, efforts to develop antibiotics and study mechanisms of resistance should be continuous, resilient, and steady.

Keywords: *Enterobacterales*, infection, beta-lactamase, beta-lactamase inhibitors, *Enterobacteriaceae*/enzymology, therapeutics.

Resumen

Las enterobacterias productoras de betalactamasas de espectro extendido se han convertido en una pandemia a nivel mundial representando una amenaza para la salud pública debido a la alta morbilidad y mortalidad asociada a las infecciones por estas, es fundamental realizar una revisión sistemática para documentar la combinación de antibióticos utilizada para combatir las infecciones, con el fin de categorizar y ordenar los tratamientos más utilizados y determinar los más efectivos. La búsqueda electrónica se realizó desde junio de 2020 hasta agosto de 2020. Las bases de datos utilizadas fueron Pubmed, Virtual Health Library, ScienceDirect y la biblioteca Cochrane; se utilizaron los siguientes Medical Subject Headings (MESH): "*Enterobacterales*", "infection", "beta-lactamase", "beta-lactamase inhibitors", "Therapeutics", "*Enterobacteriaceae*/enzymology". La búsqueda electrónica dio como resultado 1.526 artículos que cumplían los criterios generales, se excluyeron 1.493 artículos; sólo 35 artículos cumplían todos los criterios de inclusión. básicamente, no hay diferencias tangibles entre el tratamiento con antibióticos betalactámicos (ya sean combinaciones o carbapenem), fluoroquinolonas, tetraciclinas y fosfomicinas en pacientes sin ninguna resistencia antibiótica preexistente. Se requiere desarrollar antibióticos, entendiendo que ellos reaccionarán y desarrollarán resistencia (hecho evolutivo). Por lo tanto, los esfuerzos para desarrollar antibióticos y estudiar los mecanismos de resistencia deben ser continuos, resilientes y constantes.

Palabras claves: *Enterobacterales*, infección, betalactamasas, inhibidores de betalactamasas, *Enterobacteriaceae*/enzimología, terapéutica.

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Introduction

Extended spectrum beta-lactamases (ESBL) producing Enterobacterales have become pandemic worldwide representing a major public health threat due to poor outcomes and high mortality associated with infections by these bacteria [1], consequently it is essential to conduct a systematic review to document the treatment used to fight infections, in order to categorize and sort the most widely used treatments and determine the most effective ones. New therapies for the treatment of ESBL-producing bacteria during the last years has been breathtaking; nevertheless, for one successful case there are others that get complicated or the chemotherapy results unsuccessful because of the indiscriminate use of antibiotics in early ages. Resistant bacteria could exist in any environment, but its frequency is likely to rise when microorganisms increase survival capacity under selective pressure (e.g. hospitals). While there are many types of selective pressures, for the purpose of the current discussion, we will assume that the evolution of antibiotic resistance is driven primarily by the exposure to antibiotic drugs [2].

The cascade of resistance mechanisms is responsible for preventing the action of antibiotics at each step of their passage through the bacterial cell: bacteria can alter their cell wall structure to deny entry of the drug or synthesize efflux pumps to expel it; they can modify (and even destroy) compounds by producing enzymes such as beta-lactamases or stop the production of enzymes necessary for antibiotic activation; they can modify, hide or quantitatively adjust the intended drug target; or, finally, they can activate alternative metabolic pathways to circumvent the toxic action of the antibiotic [3].

During the last few decades, several bacterial pathogens have evolved into multi-drugs resistance forms. Of particular concern are multi-drugs resistance Gram-negative pathogens, such as *Enterobacterales* Order [4]. The differences between Gram-negative bacteria (GNB) and Gram-positive bacteria lie in the cell wall structure: resulting in differences in penetration and retention of chemical agents. GNB have a complex envelope, consisting of three main layers: 1. an outer membrane, containing the lipopolysaccharide/endotoxin (Gram-positive bacteria generally lack these); 2. a thin cell wall consisting of peptidoglycan with peptide chains, partially cross-linked; and 3. the cytoplasmic or inner membrane [5].

Beta-lactamases are enzymes produced by bacteria that cleave the beta-lactam ring of some antibiotic compounds, rendering otherwise effective antibiotics largely powerless[6]. ESBLs are derived from point mutations in the genes that encode common beta-lactamases such as TEM-1, TEM-2, or SHV-1 [5] and are found exclusively in gram negative bacteria, particularly the Enterobacterales family members, including the common pathogens *Escherichia coli* and *Klebsiella pneumoniae* [6].

Methods

The objective of this review is focused on the categorization of the different treatments used in the infections produced by ESBL considering the pharmacological classification to which they belong; emphasizing the antibiotic effectiveness; as well as establishing the worldwide problem that exists around multi-resistant bacteria.

The electronic search was conducted since June 2020 until August 2020. The databases used were PubMed, ScienceDirect and the Cochrane library; the following Medical Subject Headings (MESH) were used: "Enterobacterales", "infection", "beta-lactamase", "beta-lactamase inhibitors", "*Enterobacteriaceae*/enzymology", "therapeutics". Filters used in PubMed: publication year "10 years", species "human", article type "systematic review", "meta-analysis", "clinical trial", "clinical study" and "randomized controlled trial". The descriptors used in the databases were used and combined using the logical operators: "AND". No method of exclusion was applied concerning age, sex or gender. We excluded all studies conducted before 2010, that were not systematic reviews or that were not clinical trials. An exhaustive search was carried out on the Internet following the criteria mentioned above and then a compilation of the articles that adapted to them, once the texts had been selected, a first reading was carried out to classify them. After the collection, the articles were read in such a way as to detail recurrent patterns in order to categorize the information and report the results in a concise manner.

Result

The electronic search resulted in 1.526 articles meeting the general criteria, 1.495 articles were excluded; only 33 articles met all the inclusion criteria, Figure 1.

Drugs used in the treatment of infections by extended spectrum beta-lactamase-producing enterobacteria

Regarding the above evidence, it can be stated that the infections produced by Extended spectrum beta-lactamases (ESBL) producing Enterobacterales are not a rare occurrence, being the combinations of several beta-lactam antibiotics the most effective ones in the treatment of such infections, as well as of the fluorinated quinolones and tetracyclines, the second most used in the treatment of these infections. The following is the categorization of the results.

Beta-lactam Antibiotics: the β-lactam antibiotics have a bactericidal action that disrupts bacterial cell wall formation due to covalent binding to essential penicillin-binding proteins (PBPs), which are involved in the terminal steps of peptidoglycan cross-linking in both Gram-negative and Gram-positive bacteria [7]. Their commonality is the ability to hydrolyze chemical compounds containing a β-lactam ring; Gram-negative bacteria, β-lactamases have played a critical clinical role

and have served as the primary resistance mechanism for the β-lactam antibiotics [8]. With a limited number of treatment options available against multidrug-resistant Gram-negative bacteria, newer treatment strategies are becoming increasingly important [9] (Table 1).

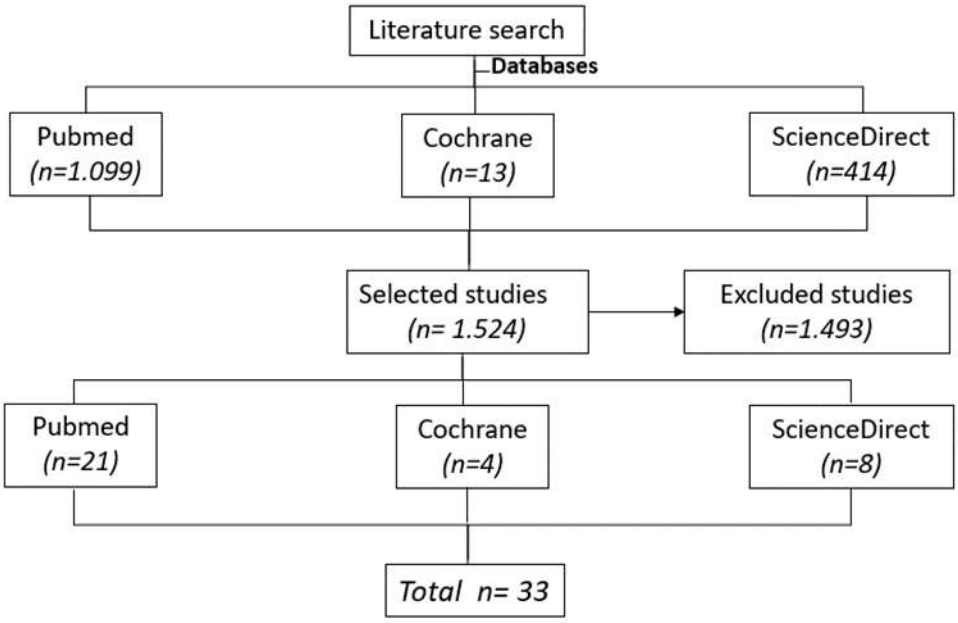

Figure 1. Flowchart depicting the selection process of studies included in the review

Table 1. Beta-lactam Antibiotics

Cite	Year/Study type	Authors	Sample	Results
8	(2018) Original article	Bush K.	A later scheme classifies - lactamases according to amino acid sequences, resulting in class A, B, C, and D enzymes. A more recent nomenclature combines the molecular and biochemical classifications into 17 functional groups.	Lactamases, some of our oldest enzymes, have emerged as perhaps the most studied, and most troublesome, of the antibiotic resistance determinants.
9	(2018) Critical Review	Chastain DB, White BP, Cretella DA, Bland CM.	Data abstracted included empirical or definitive therapy, patient population, dosing, source of infection and severity, infectious etiology, and outcome.	Completely sparing carbapenem therapy cannot be justified among patients with ESBL BSIs.

Carbapenem: have been recommended as the first-line antimicrobial agent to treat infections caused by ESBL-producing *Enterobacterales* [10-12], because they are not affected by these resistance mechanisms. In relation to definitive therapy, the overall mortality was lower with carbapenem therapy than with non-carbapenem (RR 0.78, 95% CI 0.61–0.98, I2"29%) or non-BL/BLI (RR 0.71, 95% CI 0.56–0.90, I2"22%) therapy. In contrast, there were no significant differences with respect to the overall mortality rates between the carbapenem groups and the BL/BLI (RR 0.67, 95% CI 0.37–1.20, I2"61%) [13].

An observational prospective study suggests that patients with nosocomial infections were also more frequently treated empirically with carbapenems (79.41% vs. 57.8%; OR 2.8, 95% CI 1.1–7.8) [14].

In a meta-analysis, a total of 25 observational studies describing 3842 patients were identified 1963 patients received empiric antibiotics and 1879 received definitive antimicrobial therapy, the pooled odds ratio of BL-BLI versus carbapenems mortality within 30 days for ESBL-producing Enterobacterales bloodstream infections, from random effects meta-analysis, was 1.07 but it was not clinically significant (95% CI, 0.81-1.41; P=0.63) [1].

In contrast to the other carbapenems, ertapenem was as efficacious as any other carbapenem for the treatment of bloodstream infections due to diverse ESBL-E from different sources and in different clinical situations. In fact, a study indicates that de-escalation therapy to ertapenem is non-inferior to continuation of group 2 carbapenems for clinical cure rate (%Δ = 14.0 [95% CI: -2.4

to 31.1]), microbiological eradication rate (%Δ = 4.1 [-5.0 to 13.4]), superimposed infection (%Δ = -16.5 [-38.4 to 5.3]), and 28-day mortality (%Δ = -20.0 [-39.3 to -0.8]) [11].

The current 'gold standard' treatment for ESBL-producing Gram-negative bacteremia is carbapenem. However, only limited observational data exist regarding the clinical outcome with carbapenem. Studies addressing the clinical efficacy of ertapenem are exceedingly scarce. Nevertheless, recent reports suggest favorable clinical responses after having used ertapenem against ESBL-producing organism [15] (Table 2).

Table 2. Carbapenem

Cite	Year/Study type	Authors	Sample	Results
10	(2012) Systematic review and meta-analysis	Vardakas KZ, Tansarli GS, Rafailidis PI, Falagas ME.	Twenty-one articles, studying 1584 patients, were included. *Escherichia coli* and *Klebsiella pneumoniae* were the most commonly studied bacteria. Delay in appropriate treatment up to 6 days was reported.	No statistically significant differences in mortality were found between carbapenems and BL/BLIs administered as definitive (RR 0.52, 95% 0.23-1.13) or empirical (RR 0.91, 95% CI 0.66-1.25) treatment. BL/BLIs were not associated with lower mortality than non-BL/BLIs administered either definitively (RR 1.59, 95% 0.83-3.06) or empirically (RR 0.82, 95% 0.48-1.41).
11	(2017) Open-label randomized controlled trial	Rattanaumpawan P, Werarak P, Jitmuang A, Kiratisin P, Thamlikitkul V.	*Enterobacteriaceae* infections who had received any group 2 carbapenem for less than 96 h. In the intervention group, the previously-prescribed group 2 carbapenem was de-escalated to ertapenem. In the control group, the group 2 carbapenem was continued.	During June 2011-December 2014, 32 patients were randomized to the de-escalation group and 34 to the control group. Most common sites of infection were urinary tract infection (42%). Characteristics of both groups were comparable.
12	(2016) Multinational pre-registered cohort study	Gutiérrez-Gutiérrez B, Bonomo RA, Carmeli Y, Paterson DL, Almirante B, Martínez-Martínez L, et al.	The empirical therapy cohort (ETC) and the targeted therapy cohort (TTC) included 195 and 509 patients, respectively.	Cure/improvement rates were 90.6% with ertapenem and 75.5% with other carbapenems (P¼0.06) in the ETC and 89.8% and 82.6% (P¼0.02) in the TTC, respectively; 30-day mortality rates were 3.1% and 23.3% (P¼0.01) in the ETC and 9.3% and 17.1% (P¼0.01) in the TTC, respectively. Adjusted ORs (95% CI) cure/improvement with empirical and targeted ertapenem were 1.87 (0.24-20.08; P¼0.58) and 1.04 (0.44-2.50; P¼0.92), respectively.
13	(2018) Systematic review and meta-analysis	Son SK, Lee NR, Ko JH, Choi JK, Moon SY, Joo EJ, et al.	Thirty-five publications fulfilled the inclusion criteria.	Regarding empirical therapy, there were no significant differences between the groups that received carbapenems and those that received non-carbapenems in relation to overall mortality.
14	(2015) Clinical trial	Pilmis B, Delory T, Groh M, Weiss E, Emirian A, Lecuyer H, et al.	Seventy-nine patients were included: 36 (45.6%) were children, 27 (34.1%) were hospitalized in intensive care units, and 37 (47%) were immunocompromised.	Antimicrobial resistance (44.7%), infection relapse (26.9%), and clinical instability (19.2%) were the most important reasons for not prescribing alternatives. *E. coli*-related infections appeared to be a protective factor against maintaining the carbapenem prescription (odds ratio 0.11, 95% confidence interval 0.041-0.324; p = 0.0013).
15	(2012)	Wu UI, Chen WC, Yang CS, Wang JL, Hu FC, Chang SC, et al.	This non-concurrent prospective study included adult patients with ESBL-EC bacteremia during a 2.5-year period at a 2200-bed teaching hospital.	Of 71 patients who met the study criteria, nine died within 3 days. Among the 62 remaining patients who received definitive antimicrobial therapy, 13 died within 30 days.

Ceftazidime/Avibactam: is an antibacterial agent that consists of an existing third-generation cephalosporin combined with a novel β-lactamase inhibitor. The addition of avibactam restores the activity of ceftazidime against gram-negative bacilli infections caused by MDR gram-negative organisms such as ESBL- producing Enterobacterales, MDR *P. aeruginosa*, and KPC *K. pneumoniae* [16].

A meta-analysis of three studies including 1186 patients demonstrated that there was no significant difference in the rate of clinical success between the two groups treated with CAZ- AVI versus carbapenems (RD = 0.00, 95% CI –0.0 6 to 0.0 6; P = 0.99), Only one study comprising 332 patients reported mortality and showed no statistically significant difference between the two groups (RD = 0.00, 95% CI –0.03 to 0.03; P = 0.98) [17].

Ceftazidime/avibactam at a 4:1 ratio (1 g or 2 g of ceftazidime) was effective in suppressing the growth of eight strains of ceftazidime-resistant Enterobacterales; unexpectedly, all strains were rapidly killed with growth suppression for ≥10 h when ceftazidime was dosed as a continuous infusion and avibactam was given as a single bolus dose [18].

In two identical prospective, randomized, double-blind, comparative phase 3 non-inferiority studies in patients with cIAI (RECLAIM; NCT01499290), ceftazidime-avibactam was found to be highly active in vitro against baseline Enterobacterales isolates, with an overall MIC90 of 0.25 mg/l (128-fold lower than that of ceftazidime alone) and an MIC90 of ≤2 mg/l against each of the individual members of the Enterobacterales family. These results agree with the clinical results of the Phase 3 study, which showed that ceftazidime-avibactam plus metronidazole is effective in patients with cIAI, with a clinical cure rate similar to that of meropenem in patients with Gram-negative infection [19].

In a post hoc exploratory analysis that evaluated the clinical activity of ceftazidime/avibactam against MDR Enterobacterales and *P. aeruginosa* isolates14 pooled from the ceftazidime/avibactam Phase III clinical trials, included 2585 patients from countries across North and South America, Europe, Asia and Africa, successfully demonstrated ceftazidime/avibactam to be a suitable alternative to carbapenem-based therapies for certain serious Gram-negative infections [20].

REPRISE was an international, randomized, open-label, phase 3 trial that recruited patients from hospitals worldwide. 33 patients were enrolled and randomized at 53 hospitals in 16 countries worldwide: 165 to ceftazidime-avibactam, and 168 to best available therapy. The study showed that ceftazidime-avibactam and best available therapy led to the same proportion of patients achieving an overall clinical cure at the test-of- cure visit in the mMITT population (91% in both groups) [21]. This agent replenishes the current candidate therapy for multidrug-resistant GNB pathogens, particularly ESBL-producing organisms and CRE, which is likely to be its principal role in therapy [22] (Table 3).

Ceftolozane/Tazobactam: β-Lactam/β-lactamase inhibitor combination antibiotics, have been considered a carbapenem-sparing option for treatment of ESBL producers [23]. Ceftolozane/tazobactam consists of a novel cephalosporin and an established β-lactamase inhibitor that is being developed to address antimicrobial resistance in serious infections caused by gram-negative pathogens, including complicated urinary tract infection/pyelonephritis (cUTI) and ventilated nosocomial pneumonia [24]. In vitro activity of ceftolozane/tazobactam has been confirmed against ESBL-producing Enterobacterales; in two identical multicenter, prospective, randomized, double- blind, placebo-controlled trials; In total, 993 patients were randomized to ceftolozane/tazobactam plus metronidazole (n = 487) or meropenem (n = 506), and 806 (81.2%) qualified for the MITT population. In this study, more than one- half of the ESBL-producing Enterobacterales isolated at baseline were positive for CTX-M-14 or CTX-M-15–type enzymes. Ceftolozane/tazobactam plus metronidazole maintained clinical efficacy against these highly resistant strains (100%) [25].

In Forty-four hospitals, of the 2511 Enterobacterales collected, 442 (18%) of these isolates screened positive for ESBL production, when considering only the Enterobacterales-confirmed ESBL-positive isolates in the absence of detectable carbapenemases, the rank order susceptibility of the conventional non-carbapenem agents was as follows: C/T, 82% [26].

Another randomized (1:1 ratio), double-blind, phase 3 non-inferiority trials study, clinical cure rates for patients with ESBL-ENT (including CTX-M-14/ 15), the overall clinical cure rate for ceftolozane/tazobactam against ESBL-ENT was 97.4%; clinical cure rates were high regardless of the presence/absence of CTX-M-14/15-type ESBLs. In vitro susceptibility testing showed that ceftolozane/tazobactam was at least 2-fold more potent (MIC90 values) than most antibacterial tested against ESBL-ENT [27] (Table 4)

Fluoroquinolone: quinolones target two essential bacterial type II topoisomerase enzymes, DNA gyrase and DNA topoisomerase IV. Both enzymes are heterotetramers with two subunits, gyrase being constituted as GyrA2GyrB2 and topoisomerase IV as ParC2ParE2. Quinolones inhibit enzyme function by blocking the resealing of the DNA double-strand break, but, in addition, this process stabilizes a catalytic intermediate covalent complex of enzyme and DNA that serves as a barrier to movement of the DNA replication fork or transcription complexes and can be con- verted to permanent double-strand DNA breaks, thereby functioning as topoisomerase poisons [28].

The increased use of carbapenems in response to ESBL and other resistant infections has led to the emergence of carbapenem resistance. In order to preserve carbapenems, all antibiotic options that may be available to treat ESBL- producing infections should be considered [29]. A systematic review and meta-analysis compare patient outcomes, specifically recurrence of infection and all-cause mortality, with the use of Fluoroquinolone or Trimethoprim- Sulfamethoxazole vs ß-lactams as oral step-down treatment of GNR bacteremia; findings suggest that mortality is not significantly different with use of FQ/TMP-SMX vs ß-lactams in the step-down treatment of uncomplicated GNR bacteremia. It did find, however, that overall recurrence of infection occurred more frequently with ß-lactams when compared with FQs [30].

In a study of 716 participant's fluoroquinolones were the only class of antibiotics with sufficient variation in treatment duration to explore the impact of duration on emergence of resistance. Of 76 patients receiving fluoroquinolones, 33 (43%) and 43 (57%) received short and long treatment, respectively; no epidemiologic risk factors

Table 3. Ceftazidime/Avibactam

Cite	Year/Study type	Authors	Sample	Results
16	(2016) New Drug Review	Sharma R, Eun Park T, Moy S.	Abstracts from Infectious Disease Week (2014–2015), the Interscience Conference on Antimicrobial Agents and Chemotherapy (2014–2015), and the European Congress of Clinical Microbiology and Infectious Diseases were also searched.	Ceftazidime, a third-generation cephalosporin, when combined with avibactam has a significant improvement in its activity against β-lactamase producing gram-negative pathogens, including extended spectrum β-lactamases, AmpC β-lactamases, Klebsiella pneumoniae carbapenemase-producing Enterobacteriaceae, and multidrug-resistant *Pseudomonas aeruginosa*.
17	(2019) Meta-analysis of randomized controlled trials	Che H, Wang R, Wang J, Cai Y.	Three RCTs (1186 patients) were included in the meta-analysis.	The meta-analysis showed that there were no significant differences between CAZ-AVI and carbapenems in clinical success [risk difference (RD) = 0.00, 95% confidence interval (CI) -0.06 to 0.06; P = 0.99], microbiological success (RD = 0.07, 95% CI -0.04 to 0.18; P = 0.21) or AEs (RD = 0.00, 95% CI -0.02 to 0.03; P = 0.81). SAEs with CAZ-AVI were numerically higher than with carbapenems (RD = 0.02, 95% CI -0.00 to 0.04; P = 0.06).
18	(2015) Article original	Bush K.	Lactamase inhibitors (BLIs) have played an important role in combatting -lactam resistance in Gram-negative bacteria, but their effectiveness has diminished with the evolution of diverse and deleterious varieties of -lactamases.	Because all of the inhibitor combinations are being developed as parenteral drugs, an orally bioavailable combination would also be of interest.
19	(2018) Clinical trial	Stone GG, Newell P, Bradfordc PA.	In vitro activity of ceftazidime-avibactam versus comparators was evaluated against 1,440 clinical isolates obtained in a phase 3 clinical trial in patients with complicated intra- abdominal infections (cIAI; NCT01499290). Overall, in vitro activity was determined for 803 Enterobacteriaceae, 70 P. aeruginosa, 304 Gram-positive aerobes and 255 anaerobes isolated at baseline from 1,066 randomized patients.	Ceftazidime-avibactam was highly active against isolates of Enterobacteriaceae, with an overall MIC90 of 0.25 mg/l. In contrast, the MIC90 for ceftazidime alone was 32 mg/l. The MIC90 value for ceftazidime-avibactam (4 mg/l) was one dilution lower than that of ceftazidime alone (8 mg/l) against isolates of Pseudomonas aeruginosa.
20	(2018) Phase III clinical trial program	Stone GG, Newell P, Gasink LB, Broadhurst H, Wardman A, Yates K, et al.	Baseline isolates from five Phase III randomized controlled trials of ceftazidime/ avibactam versus predominantly carbapenem comparators in patients with cIAI (RECLAIM 1 and 2; NCT01499290 and RECLAIM3;NCT01726023), cUTI (RECAPTURE 1 and 2; NCT01595438 and NCT01599806), NP including VAP (REPROVE;NCT01808092) and cIAI or cUTI caused by ceftazidime-non-susceptible Gram-negative pathogens (REPRISE; NCT01644643) were tested for MDR status and susceptibility to ceftazidime/avibactam and carbapenem based comparators using CLSI broth microdilution methodology.	In the pooled microbiologically modified ITT population, 1051 patients with MDR Enterobacteriaceae and 95 patients with MDR P. aeruginosa isolates were identified. Favorable microbiological response rates at TOC for all MDR Enterobacteriaceae and MDR P. aeruginosa were 78.4% and 57.1%, respectively, for ceftazidime/avibactam and 71.6% and 53.8%, respectively, for comparators.
21	(2016) Randomized, pathogen-directed, phase 3 study	Carmeli Y, Armstrong J, Laud PJ, Newell P, Stone G, Wardman A, et al.	Between Jan 7, 2013, and Aug 29, 2014, 333 patients were randomly assigned, 165 to ceftazidime-avibactam and 168 to best available therapy.	Of these, 154 assigned to ceftazidime-avibactam (144 with complicated urinary tract infection and ten with complicated intra-abdominal infection) and 148 assigned to best available therapy (137 with complicated urinary tract infection and 11 with complicated intra-abdominal infection) were analyzed for the primary outcome. 163 (97%) of 168 patients in the best available therapy group received a carbapenem, 161 (96%) as monotherapy.
22	(2018) Systematic review and meta-analysis	Zhong H, Zhao XY, Zhang ZL, Gu ZC, Zhang C, Gao Y, et al.	Twelve articles (4951 patients) were included, consisting of nine RCTs and three observational studies comparing CAZ-AVI with other regimens, e.g. carbapenems or colistin.	No significant differences were detected between groups in terms of mortality and adverse events. In addition, subgroup analyses demonstrated that CAZ-AVI improved clinical response (RR = 1.61; 95% CI: 1.13-2.29).

Table 4. Ceftolozane/Tazobactam

Cite	Year/Study type	Authors	Sample	Results
23	(2018) Randomized Clinical Trial	Harris PNA, Tambyah PA, Lye DC, Mo Y, Lee TH, Yilmaz M, et al.	Included hospitalized patients enrolled from 26 sites in 9 countries from February 2014 to July 2017.Of 1646 patients screened, 391 were included in the study.	A total of23 of187 patients (12.3%) randomized to piperacillin-tazobactam met the primary outcome of mortality at 30days compared with 7of 191 (3.7%) randomized to meropenem (risk difference, 8.6%[1-sided97.5%CI, to 14.5%];P = .90 for noninferiority)
24	(2015) Comparative study	Liscio JL, Mahoney M V., Hirsch EB.	An online literature search was performed using the MEDLINE database and the search terms 'ceftolozane', 'tazobactam', 'ceftazidime', 'avibactam', 'antibiotic resistance', 'beta-lactamase' and 'beta-lactamase inhibitor'. English language studies from 2009 to 2015 were considered.	Both agents appear to be well tolerated and show promise in the treatment of MDR Gram-negative infections.
25	(2015) Randomized, Double-Blind, Phase 3 Trial (ASPECT-cIAI)	Solomkin J, Hershberger E, Miller B, Popejoy M, Friedland I, Steenbergen J, et al.	993 patients were randomized to ceftolozane/tazobactam plus metronidazole (n = 487) or meropenem (n = 506), and 806 (81.2%) qualified for the MITT population.	Ceftolozane/tazobactam plus metronidazole was noninferior to meropenem in the primary (83.0% [323/389] vs 87.3% [364/417]; weighted difference, -4.2%; 95% confidence interval [CI], -8.91 to .54) and secondary (94.2% [259/275] vs 94.7% [304/321]; weighted difference, -1.0%; 95% CI, -4.52 to 2.59) endpoints, meeting the prespecified noninferiority margin.
26	(2015) Systematic review	Sutherland CA, Nicolau DP.	44 hospitals provided nonduplicate, nonurine isolates of E coli (n ¼ 1306), K pneumoniae (n ¼ 1205), and P aeruginosa (n ¼ 1257) from adult inpatients. MICs for C/T and 11 other antimicrobials were determined with broth microdilution methods.	The carbapenems, C/T, and colistin displayed the highest percentage of susceptibility and lowest MIC90 against the Enterobacteriaceae, followed by piperacillin/tazobactam (TZP), cefepime, tobramycin, aztreonam, ceftriaxone, and ciprofloxacin.
27	(2017) Clinical trial	Popejoy MW, Paterson DL, Cloutier D, Huntington JA, Miller B, Bliss CA, et al.	Of 2076 patients randomized, 1346were included in the pooled ME population and 150 of1346 (11.1%) had ESBL-ENT at baseline.	At US FDA/EUCAST breakpoints of ≤2/≤1 mg/L, 81.8%/72.3% of ESBL-ENT (ESBL-*Escherichia coli*, 95%/ 88.1%; ESBL-Klebsiella pneumoniae, 56.7%/ 36.7%) were susceptible to ceftolozane/tazobactam versus 25.3%/24.1% susceptible to levofloxacin and 98.3%/ 98.3% susceptible to meropenem at CLSI/ EUCAST breakpoints. Clinical cure rates for ME patients with ESBL-ENT were 97.4% (76/78) for ceftolozane/tazobactam [ESBL-E. coli, 98.0% (49 of 50); ESBL-K. pneumoniae, 94.4% (17 of 18)], 82.6% (38 of 46) for levofloxacin and 88.5% (23 of 26) for meropenem.

were identified for colonization by ESBL-PE, nor was fluoroquinolone treatment significantly associated with an increase in the prevalence of ESBL-PE colonization within 28 days: aPR at 1.36 (0.35−5.20) [31].

Multiple studies have analyzed occurrence of co-resistance between fluoroquinolones and ESBL production mainly in Enterobacterales. There is a high risk of fluoroquinolone resistance in ESBL- producing Gram-negative bacilli. The qnr genes, commonly found on ESBL-producing Enterobacterales, have not been linked to outright resistance, but rather confer reduced susceptibility to fluoroquinolones. In such situations, the minimum inhibitory concentration (MIC) should be taken into consideration and it may be prudent to use increased doses of fluoroquinolones. For infections at sites such as the urinary tract where ciprofloxacin and levofloxacin concentrate, selection of these agents may be more appropriate. It is important, nevertheless, to consider historical patterns of quinolone use leading to QRDR and the potential for increased resistance with continued use. Data regarding the use of fluoroquinolones, when reported as susceptible, in the treatment of ESBL-producing organisms have conflicting results [29].

Sitafloxacin, a broad-spectrum oral fluoroquinolone, is active against many gram-positive, gram-negative, and anaerobic bacteria, including strains resistant to other fluoroquinolone. A prospective, open-label, randomized, controlled trial was conducted at Ramathibodi Hospital, a

1200-bed university hospital in Bangkok, Thailand. Thirty-six patients with a presumptive diagnosis of acute pyelonephritis were enrolled. They were randomized into either the sitafloxacin group (19 patients, 52.8%) or the ertapenem group (17 patients, 47.2%). Bacterial eradication was 84.2% and 75.0% in sitafloxacin and ertapenem groups, respectively ESBL-EC infection [32].

Unfortunately, increasing in vitro resistance to quinolones in isolates which are also ESBL producers will limit the role of these antibiotics in the treatment of infections due to ESBL-producing organisms in the future [33] (Table 5).

Table 5. Fluoroquinolones

Cite	Year/Study type	Authors	Sample	Results
28	(2016) Original article	Hooper DC, Jacoby GA.	Resistance mutations in one or both of the two drug target enzymes are commonly in a localized domain of the *gyrA* and *parC* subunits of gyrase and topoisomerase IV, respectively, and reduce drug binding to the enzyme–DNA complex.	Plasmids with these mechanisms often encode additional antimicrobial resistance and can transfer multidrug resistance that includes quinolones
29	(2016) Literature Review	Wiener ES, Heil EL, Hynicka LM, Kristie Johnson J.	A total of 18 studies that analyzed fluoroquinolone resistance and association to ESBL producing bacteria from either molecular or clinical perspectives were identified.	Fluoroquinolone resistance may be co-transmitted in ESBL-producing *Enterobacteriaceae*. There are limited data on the efficacy for fluoroquinolones in the treatment of ESBL-producing infections.
30	(2019) Systematic Review and Meta-analysis	Punjabi C, Tien V, Meng L, Deresinski S, Holubar M.	Eight retrospective studies met inclusion criteria with data for 2289 patients, of whom 65% were transitioned to oral FQs, 7.7% to TMP-SMX, and 27.2% to BLs. Follow-up periods ranged from 21 to 90 days.	All-cause mortality was not significantly different between patients transitioned to either FQ/TMP-SMX or BLs (odds ratio [OR], 1.13; 95% confidence interval [CI], 0.69–1.87). Overall recurrence of infection, either bacteremia or the primary site, occurred more frequently in patients transitioned to oral BLs vs FQs (OR, 2.05; 95% CI, 1.17–3.61). Analysis limited to recurrent bacteremia was similarly suggestive, although limited by small numbers (OR, 2.15; 95% CI, 0.93–4.99).
31	(2018) Multinational prospective cohort study	Stewardson AJ, Vervoort J, Adriaenssens N, Coenen S, Godycki-Cwirko M, Kowalczyk A, et al.	We included 300 households (205 exposed, 95 non-exposed) with 716 participants.	Most exposed patients received nitrofurans (86 [42%]) or fluoroquinolones (76 [37%]). CIP-RE were identified in 16% (328/2033) of samples from 202 (28%) participants.
32	(2017) Pilot study	Malaisri C, Phuphuakrat A, Wibulpolprasert A, Santanirand P, Kiertiburanakul S.	A prospective randomized controlled trial of patients with acute pyelonephritis caused by ESBL-EC was performed as a pilot study. One of the carbapenems was initially given to the patients. After day 3, patients were randomized to receive either sitafloxacin or ertapenem.	There was no statistically significant difference in baseline characteristics between the two groups except a lower proportion of previous urinary catheter insertion in the sitafloxacin group (15.8% vs. 52.9%, p ¼ 0.018).
33	(2000) Article original	Paterson DL.	In vitro studies and observational studies strongly suggest that carbapenems (imipenem or meropenem) should be regarded as drugs of choice for serious infections due to ESBL-producing organisms. Other b-lactam antibiotics (cefepime, b-lactam/b-lactamase inhibitor combinations) are not suitable as first-line therapy.	The increasing frequency of the association between quinolone resistance and ESBL production have greatly limited the role of this class of antibiotic against ESBL producers.

Tetracyclines: many studies have indicated that the tetracyclines bind to the RNA component of bacterial ribosomes. More specifically, they are believed to inhibit translation by binding to the 16S rRNA and inhibiting the

binding of aminoacyl-tRNA to the mRNA-ribosome complex. A number of binding sites have been identified on the 16S rRNA through photoaffinity labelling and chemical foot printing, indicating certain bases as contributing to the binding pocket. Recently, another study has shown that the tetracyclines bind to double stranded RNAs of random base sequence, indicating that the double-stranded structures of RNAs may play a more important role in their interaction with the tetracyclines than the specific base sequences [34].

Eravacycline is a novel, fully synthetic antibiotic of the tetracycline class designed to be active against the 2 main acquired tetracycline-specific resistance mechanisms: ribosomal protection and active drug efflux. A randomized, double-blind, double-dummy, multicenter study using a 2-arm, with a total of 541 patients, the difference in clinical cure rates was −1.80% with a 2-sided 95% CI of −7.4% to 3.8%, meeting the statistical criteria for noninferiority. The microbiologically evaluable population also achieved statistical noninferiority, with clinical cure rates of 91.4% (181 of198) for eravacycline and 95.0% (189of199) for ertapenem (difference of −3.6%; 95% CI, −8.9% to 1.5%) [35].

Another trial compared eravacycline with ertapenem (IGNITE1), and eravacycline with meropenem (IGNITE4). Both studies were randomized, double-blind, double-dummy, multicenter, prospective studies. A total of 1041 patients were randomly assigned to receive either eravacycline or the carbapenem control drug. For the micro-ITT population, clinical cure rates were virtually identical between treatment groups in both studies: 86.8% for eravacycline versus and 87.6% for ertapenem; 90.8% for eravacycline versus 91.2% for meropenem, with overall cure rates of 88.7 and 89.3% for the pooled eravacycline and comparator groups, respectively [36].

A clinical trial compared eravacycline (1 mg/kg IV q12h) to meropenem (1 g IV q8h) for the management of complicated intra-abdominal infections. The key finding was non-inferiority of eravacycline to meropenem [37].

Eravacycline as monotherapy has demonstrated broad antimicrobial activity in both in vitro activity studies and in the two-Phase III trials completed for cIAI, each using a broad-spectrum carbapenem as a comparator. This, coupled with the improved pharmacokinetics and adverse event profile relative to older members of the tetracycline class [35] (Table 6).

Fosfomycin: previous surveys have shown that fosfomycin, a phosphonic acid derivative that disrupts cell wall synthesis, is active against 85–100% of multidrug-resistant uropathogens. Fosfomycin is active against most ESBL-producing Enterobacterales according to the current susceptibility breakpoints. Clinical and microbiological success with fosfomycin and carbapenems was not significantly different (77.8% vs. 95 and 59.3% vs. 80%, respectively; P> 0.05) [36].

A systematic review conducted in 2010 with a total of 21 studies, shows that fosfomycin has a high level of antimicrobial activity against *Enterobacterales* isolates with advanced resistance to antimicrobial drugs, such as the production of ESBLs [38].

Even though development of resistance to fosfomycin can occur during treatment, it seems to be much less frequent in E. coli than in Klebsiella spp or Pseudomonas aeruginosa, and specifically in UTI. In the same way fosfomycin trometamol is an oral formulation of fosfomycin reaching low plasma concentrations but very high urinary concentrations; the results from observational studies suggest that fosfomycin trometamol is useful for the treatment of cystitis and complicated UTIs caused by ESBL-EC [39].

In an observational study of patients with complicated UTIs due to ESBL-producing *E. coli*, oral fosfomycin was compared to carbapenem treatment. Clinical and microbiological success with fosfomycin and carbapenems was not significantly different (77.8% vs. 95 and 59.3% vs. 80%, respectively; P > 0.05) [36] (Table 7).

Discussion

The introduction of antibiotics into clinical use was arguably the greatest medical breakthrough of the 20th century. In addition to treating infectious diseases, antibiotics made many modern medical procedures possible, including cancer treatment, organ transplants and open-heart surgery [40]. However, the fear of missing covering empirical coverage is the main reason that leads clinicians to the indiscriminate use of broad-spectrum antibiotics, with the consequent negative effect on further rise in resistance rates; a systematic review shows that there are a significant association between inappropriate empirical antibiotics and the percentage of patients in the study with all resistance phenotypes tested [41].

Thus, in most of these studies, what is tested is the inappropriate prescription of antibiotics: if a 3GC is prescribed in patients with bacteria resistant to this antibiotic, they are more likely to die than if the bacteria are susceptible. This does not mean that mortality is higher with these bacteria but simply that the prescription of antibiotics was inappropriate, which is indeed more likely to occur in the case of MDR bacteria [42], but the long-time misuse and overuse of antibiotics have resulted in the widespread dissemination of antibiotics as well as antibiotic resistance genes all over the environment, not only in sewage and wastewater treatment plants, hospital effluents, aquaculture, agricultural and slaughterhouse waste, but also in surface waters, soils, and so on [43].

This research determined what antibiotics have been used in the last ten years in the treatment of infections by Enterobacteria producing extended-spectrum beta-lactamase, as well as their effectiveness by performing a systematic review of the literature; the efficacy rates achieved by Carbapenemics[6] are significantly higher compared to other beta-lactams or antibiotics belonging to another classification; also combination therapy is advisable in patients from whom an isolate with a low carbapenem minimum inhibitory concentration (8 mg/L) is

recovered, a combination regimen including high dose carbapenem is associated with better outcome [44].

Table 6. Tetracyclines

Cite	Year/Study type	Authors	Sample	Results
34	(2016) Article Original	Chukwudi CU.	Many studies have investigated the binding of the tetracyclines to the 16S rRNA using the small ribosomal subunit of different bacterial species, but there seem to be no agreement between various reports on the exact binding site on the 16S rRNA.	In the light of recent evidence that the tetracyclines bind to various synthetic dsRNAs of random base sequences, suggesting that the double-stranded structures may play a more important role in the binding of the tetracyclines to RNA than the specific base pairs as earlier speculated, it is imperative to consider possible alternative
35	(2019) Review article	Solomkin JS, Sway A, Lawrence K, Olesky M, Izmailyan S, Tsai L.	Clinical cure rates were 86.8% for eravacycline versus 87.6% for ertapenem, and 90.8% for eravacycline versus 91.2% for meropenem in the Intent to Treat (micro-ITT) populations, and 87.0% for eravacycline versus 88.8% ertapenem, and 92.4 versus 91.6% for meropenem in the Modified Intent to Treat (MITT) populations.	Eravacycline is an effective new option for use in complicated intra-abdominal infections, and in particular, for the treatment of extended-spectrum β-lactamase- and carbapenem-resistant Enterobacteriaceae-expressing organisms
36	(2018) Expert review	Sheu CC, Lin SY, Chang YT, Lee CY, Chen YH, Hsueh PR.	The clinical efficacy of piperacillin/tazobactam and cefepime on in vitro-susceptible ESBL-producing Enterobacteriaceae remains a concern. Many studies found an in vitro-in vivo discordance based on current breakpoints.	Recently, ceftolozane/ tazobactam and ceftazidime/avibactam have been approved for the treatment of complicated urinary tract infections and complicated intra-abdominal infections. The introduction of these new β-lactam/β-lactamase inhibitor combinations offer new carbapenem-sparing options for the treatment of ESBL infections
37	(2019) Comparative test	Solomkin JS, Gardovskis J, Lawrence K, Montravers P, Sway A, Evans D, et al.	A sample size of approximately 466 randomized subjects.	Eravacycline was noninferior to meropenem in the primary endpoint (177/195 [90.8%] vs 187/205 [91.2%]; difference –0.5%; 95% confidence interval [CI] –6.3 to 5.3), exceeding the prespecified margin.

β-Lactam antibiotics inhibit bacterial growth by inhibiting cell wall synthesis via binding to a series of enzymes, penicillin-binding proteins (PBPs) that synthesize and remodel peptidoglycan, they are broad spectrum and highly effective antibiotics [45] but the persistent exposure of bacterial strains to a multitude of β-lactams has induced dynamic and continuous production and mutation of β-lactamases in these bacteria, expanding their activity even against the newly developed β-lactam antibiotics [46], the downside of modifying known chemical structures is that, usually, multiple mechanisms of resistance exist for every class of antibiotics and not all relevant resistance mechanisms can be addressed by chemical modification [47].

The most effective combinations registered in that research are Ceftacidime/Avibactam and Ceftolozane/Tazobactam, which demonstrate that the use of other compounds to potentiate the antimicrobial effects of beta-lactam inhibitors is a useful option to resort to in the treatment of a patient.

It is impossible to ignore the fact that many of the previously used antibiotics have ceased to be effective due to the resistance developed by the bacteria; antibiotics such as Fluoroquinolones are rarely used for fear of developing resistance, but are considered in patients without previous exposure [29]; at the same time, specific treatments such as Eravacicline have been created to counteract specific resistances that have a high degree of effectiveness [35]; Fosfomycin in turn demonstrated great capacity for success against infections produced by Enterobacterales ESBLs [38]; there is basically no tangible difference between treatment with beta-lactam antibiotics (either combinations or carbapenem), fluoroquinolones, tetracyclines and fosfomycins in patients without any pre-existing antibiotic resistance.

The implementation of molecular methods for rapid detection of resistance mechanisms is generating an improvement in the treatment and control of infections produced by multi-resistant bacteria [48]; furthermore, understanding local epidemiology is essential in optimizing

targeted appropriate empiric therapy and strategies such as combination antibiograms offer significant promise as tools that can be used to optimize empiric therapy regimens. However, it is important that individual patient scenarios and previous antibiotic exposures are taken into account and appropriate diagnostics are performed [49].

It is required developing antibiotics, with the understanding that the microorganism will respond to them and resistance will develop (an evolutionary fact). Therefore, efforts to develop antibiotics and study mechanisms of resistance should be continuous, resilient, and steady [50].

The use of various antibiotic treatments to counteract infections by extended spectrum beta-lactamase-producing enterobacteria is losing effectiveness today; it is increasingly common to announce a new compound to be used to try to win the race against antibiotic resistance, however, the root of the problem that lies between poor clinical management of the patient and the indiscriminate use of antibiotics by them is not being addressed. However, using all the necessary tools at the time of diagnosis can counteract most antibiotic resistances, the use of antibiotics when the causative agent of infections is suspected, as well as combined antibiotic therapy are the mainstay in the fight against these infections.

Table 7. Fosfomycin

Cite	Year/Study type	Authors	Sample	Results
36	(2018) Expert review	Sheu CC, Lin SY, Chang YT, Lee CY, Chen YH, Hsueh PR.	The clinical efficacy of piperacillin/tazobactam and cefepime on in vitro-susceptible ESBL-producing Enterobacteriaceae remains a concern. Many studies found an in vitro-in vivo discordance based on current breakpoints.	Recently, ceftolozane/ tazobactam and ceftazidime/avibactam have been approved for the treatment of complicated urinary tract infections and complicated intra-abdominal infections. The introduction of these new β-lactam/β-lactamase inhibitor combinations offer new carbapenem-sparing options for the treatment of ESBL infections
38	(2010) Systematic review	Falagas ME, Kastoris AC, Kapaskelis AM, Karageorgopoulos DE.	17 antimicrobial-susceptibility studies were found and included in our Review, accounting for 5057 clinical isolates of Enterobacteriaceae with advanced resistance to antimicrobial drugs (4448 were producers of ESBL); 11 of the 17 studies reported that at least 90% of the isolates were susceptible to fosfomycin.	Initial clinical data support the use of fosfomycin for the treatment of urinary tract infections caused by these pathogens, although further research is needed.
39	(2015) Research protocol for a randomized controlled trial	Rosso-Fernández C, Sojo-Dorado J, Barriga A, Lavín-Alconero L, Palacios Z, López-Hernández I, et al.	Hospitalised adults (18 years of age or older) with bacteraemic UTI caused by fosfomycin and meropenem susceptible ESBL-EC are candidates to be included in the study. Eligible	Data will be presented at international conferences and published in peer-reviewed journals.

Conflict of Relations and Activities

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ADCS: conceptualization, methodology, software, formal analysis, investigation, resources, data curation, drafting-preparation of the original draft, writing-review and editing, visualization, supervision, planning and execution, project administration. **MGJA:** conceptualization, software, investigation, resources, drafting-preparation of the original draft, writing-review and editing, visualization, supervision, planning and execution, project administration