



Review

New Agents Are Coming, and So Is the Resistance

J. Myles Keck ^{1,*} , Alina Viteri ¹ , Jacob Schultz ^{2,†}, Rebecca Fong ³, Charles Whitman ³, Madeline Poush ¹ and Marlee Martin ¹¹ Department of Pharmacy, University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA² Independent Researcher, Thonotosassa, FL 33592, USA³ Department of Pharmacy, Central Arkansas Veterans Healthcare System, Little Rock, AR 72205, USA

* Correspondence: jmkeck@uams.edu

† Work completed while employed at East Tennessee State University, Johnson City, TN 37614, USA.

Abstract: Antimicrobial resistance is a global threat that requires urgent attention to slow the spread of resistant pathogens. The United States Centers for Disease Control and Prevention (CDC) has emphasized clinician-driven antimicrobial stewardship approaches including the reporting and proper documentation of antimicrobial usage and resistance. Additional efforts have targeted the development of new antimicrobial agents, but narrow profit margins have hindered manufacturers from investing in novel antimicrobials for clinical use and therefore the production of new antibiotics has decreased. In order to combat this, both antimicrobial drug discovery processes and healthcare reimbursement programs must be improved. Without action, this poses a high probability to culminate in a deadly post-antibiotic era. This review will highlight some of the global health challenges faced both today and in the future. Furthermore, the new Infectious Diseases Society of America (IDSA) guidelines for resistant Gram-negative pathogens will be discussed. This includes new antimicrobial agents which have gained or are likely to gain FDA approval. Emphasis will be placed on which human pathogens each of these agents cover, as well as how these new agents could be utilized in clinical practice.

Keywords: antimicrobial resistance; antimicrobial stewardship; infectious diseases; multi-drug resistance; global health; antibiotics



Citation: Keck, J.M.; Viteri, A.; Schultz, J.; Fong, R.; Whitman, C.; Poush, M.; Martin, M. New Agents Are Coming, and So Is the Resistance. *Antibiotics* **2024**, *13*, 648. <https://doi.org/10.3390/antibiotics13070648>

Academic Editors: Juan Manuel Vázquez-Lago, Ana Estany-Gestal and Angel Salgado-Barreira

Received: 25 June 2024

Revised: 10 July 2024

Accepted: 11 July 2024

Published: 13 July 2024



Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

In 2010, the Infectious Diseases Society of America (IDSA) developed the “10 × 20” initiative to prompt pharmaceutical companies to develop 10 new antibiotics by 2020 [1]. As a result, over 14 new antibiotics have since gained Food and Drug Administration (FDA) approval [1–3]. Despite these advances, a growing concern for resistant pathogens remains an epidemiological focal point both domestically and internationally [4]. In 2019, the United States Centers for Disease Control and Prevention (CDC) issued an Antibiotic Resistance Threats Report that highlighted growing resistance in numerous fungal and bacterial pathogens [1]. Featured within this document, carbapenem-resistant *Enterobacteriales* (CRE) and carbapenem-resistant *Acinetobacter* (CRAB) were classified as urgent threats, which are the highest-level global threats. In light of the growing concern for antimicrobial resistance, focus has been placed on the development of new anti-infective agents that cover extended-spectrum beta-lactamases (ESBL), CRE, CRAB, and Ambler class B beta-lactamase-producing bacteria (MBL) [2,4–6].

Requirements have been established by the CDC, Centers for Medicaid and Medicare Services (CMS), and The Joint Commission (TJC) to combat the global antimicrobial resistance (AMR) pandemic [7–9]. All hospitals within the United States (U.S.) are now required to report both antimicrobial use (AU) and AMR data to the National Healthcare Safety Network (NHSN). Additionally, the CDC now mandates that all U.S. hospital systems have a designated individual(s) (i.e., medical provider, pharmacist, or both) to lead all

antimicrobial stewardship (AMS) efforts within the institution. These efforts should consist of developing and implementing AMS treatment guidelines/protocols, communicating and collaborating with medical staff, and providing competency-based training and education. Lastly, the CDC recommends that hospital systems provide adequate funding to AMS efforts to ensure all TJC and CMS standards are met [7–9].

As multi-drug-resistant (MDR) infection rates rise, the rapid diagnosis and treatment of resistant infectious processes are vital to ensure a higher probability of clinical success [10–17]. Historically, diagnostic workup and treatment of patients included medical examination by a licensed provider and determination to use antibiotics was informed solely by culture-driven selection of an antimicrobial agent [18]. However, today, antibiotic selection has become increasingly convoluted due to the widespread use of extended-spectrum Gram-negative agents [19,20]. For example, pathogens such as CRAB have extremely limited treatment options, with some being associated with dose-limiting toxicities [21–23]. To further complicate matters, not all institutions have rapid diagnostic tools at their disposal. Without the capability for internal rapid diagnostic testing, outside microbiological testing must be utilized therefore significantly delaying the time to diagnosis, and ultimately the time to targeted treatment [14,16,24–28]. Lastly, diagnostic stewardship has become a major focus in combating the increasing AMR crisis. Data have shown that inappropriate diagnostic testing can lead to both the unnecessary prescribing of antibiotics and delays in appropriate antibiotic therapy. Therefore, it is imperative that clinicians utilize the correct test in the appropriate clinical scenarios in order to avoid inappropriate prescribing of antibiotics and/or delays in targeted therapy [29–32].

This review will highlight the global AMR pandemic and will discuss the current IDSA MDR guidance documents as well as potential antimicrobial agents on the horizon.

2. New Guidance Documents Have Been Established

In 2023, the IDSA published updated guidance documents for the treatment of antimicrobial-resistant Gram-negative infections [23]. The major pathogens highlighted in this document were ESBL-producing *Enterobacteriales* (ESBL-E), AmpC-producing *Enterobacteriales* (Amp-C-E), CRE, *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-P), CRAB, and *Stenotrophomonas maltophilia* (*S. maltophilia*). The treatment recommendations from the guidance documents will briefly be discussed further for ESBL-E, CRE, and CRAB.

2.1. ESBL-E

Oxyimino cephalosporins were introduced to the market in the early 1980s, and by the late 1980s/early 1990s, reports of ESBL-E began to emerge [33]. Once considered a healthcare-acquired infection, ESBL-E is now commonly seen in the community setting [34]. This shift has led to the global rise of infections involving ESBL-E, and genetic mobilization of resistance patterns has become a major focal point in epidemiological and global health programs. Without a solution to slow the rapid global dispersion of ESBL-E isolates, rates of infections involving these pathogens will continue to rise [17,33,35].

In 2007, Melzer and colleagues prospectively collected clinical and microbiological data on adult patients with *Escherichia coli* (*E. coli*) bacteremia. These authors determined that patients with *E. coli* bacteremia had increased mortality rates. They concluded that delays in the initiation of appropriate antibiotic therapy in these patients were associated with worse clinical outcomes including death [36]. This study highlights the importance of early recognition of infections involving ESBL-E, although this idea has been recently challenged without mirrored results [37]. Regardless of mortality risk, limitations such as inaccessibility to rapid diagnostics, continue to be a challenge for many healthcare systems globally. Therefore, many clinicians are left to rely on the use of common susceptibility patterns (carbapenem and cephamycin susceptibility generally remain intact) rather than highly specific genotypic data to guide therapy. Consequently, this practice may result in prolonged durations of non-targeted or inappropriately targeted antimicrobial ther-

apy [12,38]. Due to growing rates of AMR, the implementation of rapid diagnostics and their potential benefit will remain a focal point in clinical practice [28,39–43].

Treatment of ESBL-E is dependent on the source of infection. Treatment approaches for cystitis can range from oral options such as fosfomycin to one-time doses of an aminoglycoside. Treatment options for infections outside of the bladder are limited, and most clinicians favor carbapenems, particularly for bacteremia. However, there is still debate among providers regarding the usage of fluoroquinolones and/or trimethoprim-sulfamethoxazole (TMP-SMX) to prevent carbapenem exposure [23]. For more details on ESBL-E, refer to Table 1.

Table 1. IDSA Pathogen and Drug Summary.

	ESBL-E	CRE	CRAB	DTR Pseudomonas
Common Pathogens Harboring Beta-lactamase	<i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Klebsiella oxytoca</i> , <i>Proteus mirabilis</i>	<i>Klebsiella pneumoniae</i> , <i>Escherichia coli</i> , <i>Proteus mirabilis</i>	<i>Acinetobacter baumannii</i>	<i>Pseudomonas aeruginosa</i>
CDC Threat Level	Serious	Urgent	Urgent	Serious
Common Phenotype	Resistant to ceftriaxone	Resistant to meropenem or ertapenem	Resistant to carbapenems	Resistant to Psa covering cephalosporins and/or carbapenems
Common Genotype (Ambler Class)	CTX-M-15, GES-1, SHV-2 (A)	KPC-2, IMI-1, SME-1 (A/D)	OXA-48, OXA-51, OXA-23/24 (A/C/D)	AmpC, OXA-10, VIM, GES (A/B/C/D)
Cystitis Treatment (mild infection)	Oral (PO) 1. Nitrofurantoin 2. TMP-SMX 3. FQ (ciprofloxacin, levofloxacin) 4. Fosfomycin (<i>E. coli</i> only) Intravenous (IV) 1. Carbapenem (ertapenem, meropenem, imipenem-cilastatin) 2. Single dose of aminoglycoside (tobramycin or gentamicin)	Oral (PO) 1. Nitrofurantoin 2. TMP-SMX 3. FQ (ciprofloxacin, levofloxacin) Intravenous (IV) 1. Single dose of aminoglycoside (tobramycin or gentamicin) (CR/MDR infection) 2. Ceftazidime-avibactam (CR infection) 3. Meropenem-vaborbactam (CR infection) 4. Imipenem-cilastatin-relebactam (CR infection) 5. Cefiderocol (CR/MBL/MDR infection) 6. Colistin/polymyxin B (MDR infection)	Intravenous (IV) 1. High dose ampicillin-sulbactam (up to 27 g/day) 2. Sulbactam-durlobactam 3. Cefiderocol (MDR/MBL)	Oral (PO) 1. FQ (ciprofloxacin, levofloxacin) Intravenous (IV) 1. Cefepime (not CR) 2. Piperacillin-tazobactam (not CR) 3. Ceftazidime (not CR) 4. Carbapenem (meropenem, imipenem-cilastatin) 5. Aztreonam (not CR/combination for MBL with avibactam) 6. Aminoglycoside (tobramycin, amikacin) 7. Ceftolozane-tazobactam (CR infection) 8. Ceftazidime-avibactam (CR infection) 9. Imipenem-cilastatin-relebactam (CR infection) 10. Cefiderocol (CR/MBL/MDR infection) 11. Colistin/polymyxin B (MDR infection)

Table 1. Cont.

	ESBL-E	CRE	CRAB	DTR <i>Pseudomonas</i>
Non-Cystitis Treatment (moderate-severe infection)	Oral (PO) 1. TMP-SMX 2. FQ (ciprofloxacin, levofloxacin) Intravenous (IV) 1. Carbapenem (meropenem, imipenem-cilastatin, ertapenem) 2. Aminoglycoside (tobramycin, gentamicin, amikacin) (CR/MDR infection) 3. Ceftolozane-tazobactam (CR infection) 4. Ceftazidime-avibactam (CR infection) 5. Imipenem-cilastatin-relebactam (CR infection) 6. Cefiderocol (CR/MBL/MDR infection) 7. Eravacycline (cIAI) 8. Colistin/polymyxin B (MDR infection)	Oral (PO) 1. TMP-SMX 2. FQ (ciprofloxacin, levofloxacin) Intravenous (IV) 1. Ceftazidime-avibactam (CR infection) 2. Meropenem-vaborbactam (CR infection) 3. Imipenem-cilastatin (CR infection) 4. Cefiderocol (CR/MBL/MDR infection) 5. Aminoglycosides (tobramycin, gentamicin, or amikacin) (CR/MDR infection)	Intravenous (IV) 1. High dose ampicillin-sulbactam (up to 27 g/day) in combination with another active agent 2. (cefiderocol, polymyxin B, minocycline, tigecycline) 3. Sulbactam-durlobactam	Oral (PO) 1. FQ (ciprofloxacin, levofloxacin) Intravenous (IV) 1. Carbapenem (meropenem, imipenem-cilastatin) 2. Aztreonam (not CR/MBL in combination with avibactam) 3. Aminoglycoside (tobramycin, amikacin) 4. Ceftolozane-tazobactam (CR infection) 5. Ceftazidime-avibactam (CR infection) 6. Imipenem-cilastatin-relebactam (CR infection) 7. Cefiderocol (CR/MBL/MDR infection) 8. Colistin/polymyxin B (MDR infection)

Abbreviations: ESBL-E (extended-spectrum beta-lactamase-producing *Enterobacteriales*); cIAI (complicated intra-abdominal infection); CR (carbapenem-resistant); CRAB (carbapenem-resistant *Acinetobacter baumannii*); CRE (carbapenem-resistant *Enterobacteriales*); CTX-M (cefotaxime-hydrolyzing beta-lactamase isolated in Munich); DTR (difficult-to-treat resistance); g/day (grams per day); GES (Guiana-Extended-Spectrum); IMI (imipenem-hydrolyzing beta-lactamase); IV (intravenously); KPC (*Klebsiella pneumoniae* carbapenemase); MBL (metallo- β -lactamase); MDR (multi-drug resistant); OXA (oxacillinase); PO (by mouth); Psa (*Pseudomonas*); SHV (sulfhydryl reagent variable); SME (*Serratia marcescens* enzymes); TMP-SMX (trimethoprim-sulfamethoxazole); VIM (verona integron-encoded metallo- β -lactamase).

2.2. CRE

CRE is classically defined by the CDC as an isolate demonstrating resistance to at least one of the carbapenem antibiotics (ertapenem, meropenem, doripenem, and/or imipenem) or producing a carbapenemase [44]. The discovery of CRE dates back to 1996, the year in which meropenem gained FDA approval for complicated skin and skin structure infections [45]. Numerous enzymes have emerged that elicit carbapenem resistance; however, *Klebsiella pneumoniae* carbapenemase (KPC) remains the major enzyme responsible for CRE in the U.S. [5,45]. Treatment of CRE has gained global attention for drug development and numerous agents have come to the market targeting CRE, including ceftazidime-avibactam (CTZ-AVI), meropenem-vaborbactam (MV), and imipenem/cilastatin/relebactam (ICR) [23,44]. However, Gram-negative coverage gaps remain as many of these newer agents failed to fill a niche clinical role [46]. Addition-

ally, resistance to newer Gram-negative broad-spectrum antibiotics, such as CTZ-AVI, is increasing and few options are currently available to treat these resistant pathogens [47,48].

Detection of CRE presents many challenges, with the greatest being the lack of rapid antimicrobial susceptibility testing (AST) in many national institutions [49–52]. Given the delays in microbiological results in organizations without rapid AST, many patients are empirically placed on broad-spectrum antibiotics until susceptibility reports are obtained. This may be problematic as patients who do not presently have an infection involving an MDR pathogen can have both alterations in their gut microbiota and an increased risk of future MDR infections [53–55]. Conversely, patients with an acute infection involving an MDR pathogen (i.e., CRE) will have major delays in therapy which can result in worse clinical outcomes for the patient [12,56,57].

CRE treatment, like ESBL-E, is dependent on the source of infection. The treatment for cystitis can range from oral options such as TMP-SMX, fluoroquinolones, and fosfomycin. A one-time parenteral dose of an aminoglycoside is also an alternative option for cystitis. Treatment beyond cystitis has limited options, and most clinicians favor newer antimicrobial agents such as CTZ-AVI or MV, although fluoroquinolones and TMP-SMX may have clinical roles as well depending on the source of infection [23]. For more details on CRE, refer to Table 1.

2.3. CRAB

CRAB has historically been considered a low-virulence pathogen; however, over the last two decades, it has emerged as a major global threat, predominantly due to its increasing drug resistance [58,59]. The decision to treat CRAB is often centered around colonization versus contributing pathogen [59]. If treatment is warranted, limited options are available, most of which have dose-limiting toxicities [59,60]. The recent attention on CRAB treatment has led to the FDA approval of sulbactam-durlobactam for the treatment of pneumonia involving CRAB [61].

Detection of CRAB is often straightforward and commonly involves both culture and AST [23,62–65]. Once identified, additional susceptibility reports are often needed for agents not routinely tested via AST (i.e., cefiderocol, sulbactam-durlobactam, minocycline). The treatment of CRAB is dependent on the level of illness severity, with severely ill patients likely needing two or more agents with susceptibility to the CRAB isolate [23]. For respiratory tract infections, a high dose (27 g/day) of ampicillin-sulbactam and tetracyclines remain the focal point of therapy [23,60]. Additional options for respiratory tract infections include aminoglycosides, cefiderocol, polymyxin-B, sulbactam-durlobactam, and possibly fluoroquinolones. Of these options, cefiderocol and sulbactam-durlobactam have gained favor in clinical practice. This likely stems from their favorable side effect profile compared to the other agents listed [23,60,61,66]. However, clinical trials comparing sulbactam-durlobactam vs. cefiderocol for the treatment of CRAB have not been completed. Nonetheless, it is debatable if cefiderocol should be utilized as a first line agent for CRAB as data has surfaced demonstrating the development of cefiderocol resistance during treatment for infections involving CRAB [67–69]. Additionally, initial data from the CREDIBLE-CR trial was not in support of using cefiderocol over best available therapy (BAT), although subsequent data, including a meta-analysis involving the CREDIBLE-CR trial, has argued against this conclusion [70,71]. With sulbactam-durlobactam gaining favor as a first-line therapy in moderate to severe infections involving CRAB, the future usage of cefiderocol for this indication should be reserved for MDR infections [66,72].

For chronic wound infections, treatment options mirror those seen in respiratory tract infections, and shorter durations of therapy are preferred in most clinical scenarios [73]. However, as previously mentioned, colonization vs. true pathogen is often discussed in clinical practice, especially for non-sterile sites of infection [60,73]. For more details on CRAB, refer to Table 1.

3. Epidemiology of Bacterial Resistance in the U.S. and Globally

3.1. Ambler Classification

In order to understand the landscape of resistance, it is crucial to grasp the major mechanisms bacteria use to gain resistance. Mechanisms of resistance can be broadly placed into four categories: enzymatic inactivation, porin channel loss, target modification, and efflux pumps [74–76]. Although all four mechanisms are important, this review will primarily focus upon enzymatic reactions, specifically beta-lactamases.

Enzymatic inactivation, caused by beta-lactamases, can be functionally categorized via either the Ambler classification system or the Bush-Jacoby-Medeiros classification system [77–81]. For the purpose of simplification, the Ambler class will be discussed. The Ambler class is broken into four major classes: A–D. Beta-lactamases are divided into these four main classes based on their amino acid sequences and functional characteristics. Each class encompasses distinct mechanisms of resistance, substrate specificities, and clinical implications [78,80,81]. A summary table of the Ambler classification system can be seen in Table 2.

Table 2. Ambler Classification System.

Class	Catalytic Center	Examples (Enzymes)	Substrate (Target)	Inhibited by (Treatment)
A	Serine	TEM-1, SHV-1 (penicillinases)	Penicillins	<ul style="list-style-type: none"> Amoxicillin-clavulanic acid Ampicillin-sulbactam Most cephalosporins
		CTX-M (ESBL)	Cephalosporins	<ul style="list-style-type: none"> Piperacillin-tazobactam (cystitis) Cefepime (cystitis) Carbapenems Fluoroquinolones
		KPC (Carbapenemases)	Carbapenems	<ul style="list-style-type: none"> Ceftazidime-avibactam Meropenem-vaborbactam Imipenem-cilastatin-relebactam Cefiderocol Fluoroquinolones
B	Zinc	IMP, VIM, NDM	All beta-lactam antibiotics (not aztreonam)	<ul style="list-style-type: none"> Aztreonam + avibactam Cefiderocol Cefepime-taniborbactam (not FDA approved) Xeruborbactam (not FDA approved)
C	Serine	AmpC	Penicillins and most cephalosporins	<ul style="list-style-type: none"> Cefepime Carbapenems Fluoroquinolones
D	Serine	OXA	Penicillins, cephalosporins, and carbapenems (depends on OXA subtype)	<ul style="list-style-type: none"> Amoxicillin-clavulanic acid Ampicillin-sulbactam Piperacillin-tazobactam Ceftazidime-avibactam (OXA-48) Cefiderocol (OXA-48) Fluoroquinolones

Abbreviations: CTX-M (cefotaxime-hydrolyzing beta-lactamase isolated in Munich), IMP (active on imipenem) (imipenem-hydrolyzing beta-lactamase); KPC (*Klebsiella pneumoniae* carbapenemase); NDM (New Delhi metallo-beta-lactamase); OXA (oxacillinase), SHV (Sulphydryl reagent variable); TEM (Temoneira); VIM (Verona integron-encoded metal-beta-lactamase).

Class A beta-lactamases are often referred to as “penicillinases” and are commonly found in Gram-negative bacteria such as *E. coli* and *Klebsiella pneumoniae*. These enzymes predominantly hydrolyze penicillins and cephalosporins and are inhibited by clavulanic

acid. Notable examples include the widely studied temonera (TEM) and sulfhydryl reagent variable (SHV) enzymes, which played a significant role in the development of resistance to beta-lactam antibiotics [23,78,80,82].

Class B beta-lactamases, also known as metallo-beta-lactamases (MBLs), require divalent metal ions, specifically zinc, for their catalytic activity. Unlike other classes, class B enzymes are inhibited by metal chelators such as ethylenediaminetetraacetic acid (EDTA). MBLs are commonly associated with MDR Gram-negative pathogens, including *P. aeruginosa* and *Acinetobacter baumannii* (*A. baumannii*). Their ability to hydrolyze a broad range of beta-lactam antibiotics, including carbapenems, poses a serious therapeutic challenge in clinical settings [23,78,80,82–84].

Class C beta-lactamases, or cephalosporinases, exhibit a broad substrate profile, hydrolyzing cephalosporins and penicillins. These enzymes are often chromosomally encoded and contribute to resistance in Enterobacteriaceae such as *Enterobacter cloacae* and *Citrobacter freundii*. Additionally, some penicillins and cephalosporins are strong inducers of Class C beta-lactamases, specifically AmpC, and can lead to phenotypic changes post-exposure. Due to this inducible nature, beta-lactams that are both strong inducers of AmpC and strong substrates are often avoided in practice to prevent phenotypic changes that can render certain beta-lactams ineffective. Lastly, class C beta-lactamases are not inhibited by clavulanic acid but can be inhibited by certain BLIs such as tazobactam. However, in clinical practice, cefepime, carbapenems, and fluoroquinolones have become mainstays of treatment for pathogens thought to harbor AmpC [23,78,80,82,85,86].

Class D beta-lactamases, also known as oxacillinases (OXA), primarily hydrolyze oxacillin and cloxacillin, conferring resistance to penicillins and cephalosporins. They are commonly found in Gram-negative pathogens like *Acinetobacter* spp. and *Pseudomonas aeruginosa* (*P. aeruginosa*). Class D enzymes are often associated with intrinsic resistance in these organisms and contribute to the challenge of treating infections caused by MDR strains. Furthermore, in the United States, OXA-48 has become a major concern for the development of CRE, and few treatment options are currently available that specifically target OXA-48 [23,80,87,88].

3.2. How Does Global Resistance Occur and Spread

The burden of AMR has brought upon the need for global One Health perspectives [89,90]. The concept of One Health involves human health, animal health and environmental determinants at the local, national, and global levels to understand the complex interactions between them. By understanding these complex relationships, and their interdependency, approaches can be taken to optimize the health of people, animals, and ecosystems [90]. This tactic is vital when evaluating opportunities to slow the spread of MDR pathogens as AMR is a multifaceted process involving human medicine, wildlife health, environmental health, and health economics [1,90,91]. Data have demonstrated that AMR is a complex issue that involves overprescribing and overutilization of antibiotics in both humans and animals, and without a long-term shift towards eliminating unnecessary antibiotic usage in both, AMR rates will continue to rise globally [92,93].

To illuminate the influence of antibiotic use upon the global bacterial resistome, the animal–human–environment interface is crucial to investigate [92,93]. Notably, antimicrobials have a wide array of uses within plants and animals (i.e., domestic pets, livestock, fish hatcheries, and bee hives) in addition to human applications [93,94]. Many antimicrobial drug classes used for human populations are also prescribed for animals, which includes important human medicinal classes such as fluoroquinolones or broad-spectrum beta-lactams [92]. Additionally, persistence of antibiotic residues may be seen in wastewater treatment plants, livestock or wildlife waste, coastal waters, soil, and other environmental sources [95–97]. This has created a high-pressure system and ultimately the selection of bacterial resistance [94].

A myriad of pathways exist for the environmental conferral of AMR genes [75,91,92,98,99].

These pathways range from resistant zoonotic bacteria in soil infecting fruits, vegetables, and plants to agricultural antimicrobial applications transmitting antibiotic-resistant fungi to humans [94]. Additionally, compromise of aquaculture water sources may lead to residual antimicrobial compounds via fish products or excreta of fish, culminating in rapid spread leading to selective pressure for AMR genes [94,100,101]. Regardless of the source, it is imperative that environmental origins of resistance be identified so solutions can be created and mandated to slow the spread of AMR. This will likely require cumulative collaborative efforts among multiple experts including veterinarians, physicians, allied health professionals, and laboratorians. Additionally, tackling this global human health crisis will require establishing strong strategic partnerships between all nation-states with a targeted approach to prevent and control zoonotic and emerging infectious diseases [89,90,92–94].

3.3. The Burden of Global Resistance

Based on predictive statistical modeling across 204 countries and territories in 2019, an estimated 4.95 million deaths were associated with bacterial AMR [17]. Specifically, approximately 1.27 million deaths were directly attributable to bacterial AMR [17]. Within high-income countries (HICs) using the U.S. as an example, 60,813 (95% UI: 32,520–102,231) deaths were associated with bacterial AMR, and 14,987 (95% UI: 7712–25,156) deaths were attributable to AMR in 2019 [102]. *Staphylococcus aureus* (*S. aureus*) and *E. coli* were incriminated for most of these deaths with a high degree of resistance found among multiple antibiotic classes (up to 50% resistance associated with macrolides; 38% attributed to fluoroquinolones) [102]. Within low-income countries (LMICs), using Mali as an example, 7100 deaths were attributable to AMR with 29,700 deaths associated with AMR in 2019 [103]. Notably, mortality from AMR in Mali is higher than deaths from nutritional deficiencies, enteric infections, tuberculosis and respiratory infections, neglected tropical diseases and malaria, and cardiovascular diseases [104].

Both HICs and LMICs contribute to the global antibiotic resistance profile among bacterial populations colonizing humans, pets, livestock, and/or wildlife in various ways [105,106]. Additionally, AMR comes with negative implications and multiple studies have reported on the increased morbidity and mortality related to bacterial AMR within HICs and LMICs [107–109]. Moreover, specific bacterial species have been implicated as frequently causing pathology in humans—these are termed ‘ESKAPE’ pathogens (i.e., *Enterococcus* spp., *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, and *Enterobacter* spp.) [110–112]. Particularly concerning within LMICs are ‘MDR-ESKAPE’ pathogens. These pathogens have been cited as the primary source of morbidity and mortality among bloodstream infections in hospital settings [113]. Lastly, AMR bacteria, particularly MDR-ESKAPE pathogens, have been identified as high-risk indicators for increased economic costs among both LMICs and HICs [113]. This was emphasized in 2017 when The World Bank models estimated that a high burden of AMR could raise health cost over one trillion dollars, highlighting the potential economic shortcomings that could arise if AMR rates are not slowed dramatically [114].

In 2024, the World Health Organization (WHO) released a bacterial priority pathogen report highlighting resistant trends for specific pathogens. Results from this report mirror those above. Specifically, carbapenem-resistant (CR) *Klebsiella pneumoniae* and third generation cephalosporin-resistant (3GCR) *Escherichia coli* were both labeled as a level five threat, which is the highest level given for global resistant dispersion trends. Additionally, global resistance levels were highest for *Klebsiella pneumoniae*, with over 30% of the isolates globally being labeled as CRE. Similar results were seen for CR *Escherichia coli* and 3GCR *Klebsiella pneumoniae*, although overall resistance percentage levels were lower. Lastly, resistant pathogens per million people was highest with 3GCR *Escherichia coli* (>10,000 cases); however, the number of cases per million people for CR *Escherichia coli* and 3GCR *Klebsiella pneumoniae* were above 5000. Together, these results illustrate the growing global AMR crisis [115].

3.4. Future Global Challenges with AMR

The global epidemiology of AMR presents a complex and evolving challenge to public health systems worldwide [17,116,117]. As previously discussed, the overuse and/or misuse of antimicrobial agents in human health, animal agriculture, and the environment have fueled the emergence and spread of resistant pathogens [91,118,119]. This phenomenon is exacerbated by factors such as inadequate infection prevention and control measures, poor access to clean water and sanitation facilities, and the globalization of travel and trade [91,118]. Consequently, AMR has become a pressing concern across diverse geographic regions and socioeconomic settings threatening the effectiveness of currently employed antibiotics [117].

Several key trends characterize the global epidemiology of AMR. To begin with, MDR pathogens, which exhibit resistance to multiple classes of antimicrobial agents, are increasingly prevalent and pose a significant clinical challenge [4,17]. Examples include MDR strains of *Mycobacterium tuberculosis*, methicillin-resistant *Staphylococcus aureus* (MRSA), CRE, CRAB, and MBL-producing pathogens [17]. Secondly, AMR disproportionately affects vulnerable populations (i.e., children, the elderly, and individuals with underlying health conditions) leading to higher rates of morbidity, mortality, and healthcare-associated infections [17,105,106,117,120–122]. Lastly, the emergence of extensively drug-resistant (XDR) and pan drug-resistant (PDR) strains represents a critical threat to global public health preparedness and response efforts [123,124].

Moving forward, targeted efforts to combat AMR should include supporting programs involved in the implementation of comprehensive AMS programs to promote the judicious use of antibiotics in healthcare settings, enhancing surveillance systems to monitor the spread of resistant pathogens and the identification of emerging resistance patterns, and investing in research and development of new antimicrobial agents and alternative treatment modalities [10,42,91,117,118,124–133]. Additionally, strengthening healthcare infrastructure, improving access to vaccines and basic healthcare services, and promoting interdisciplinary collaboration and international cooperation are essential to mitigate the impact of AMR and safeguard the effectiveness of antimicrobial therapy for future generations [106,127,132,134–136]. Likewise, enhancing awareness on environmental factors driving AMR is critical, and every effort should be made to decrease unnecessary antibiotic usage to help prevent both the acquisition and spread of resistant pathogens [98,132,137,138].

4. The Future of Drug Development

The need for novel antibiotics has never been greater, but outdated research and design methods, scarce governmental incentives for antibiotic development, and drug manufacturers' inability to meet profit margins for newly launched antibiotics have stunted the manufacturing of new antibiotics [125,126,128,131,139–146]. To further compound these issues, hospital reimbursement measures often fail to account for the cost of treating MDR pathogens [145,147–149]. This places strain on the hospital administration as a balance between the cost of therapy and patient care must be delicately weighed. Governmental standards have also placed a great emphasis on controlling the spread of resistant pathogens by requiring strict infection prevention and AMS practices in all hospital systems in the U.S. [9,150,151]. Countries outside the U.S. have also placed value in AMS practices, placing focus on antibiotic usage both environmentally and in clinical practice [118,152–154]. Ultimately, to combat both AMR and the lack of novel antibiotic development, the fractured relationships between pharmaceutical industry and hospital administration must become a discussion point among key decision makers. Without reimbursement reform, improved drug and research development, and adequately funded global health programs which focus on the prevention of global dispersion of MDR pathogens, the future of novel antibiotic development and utilization will become further jeopardized [91,93,130,145,155–159].

Discussed below are the recent antibiotics under development and/or recently FDA-approved for usage in clinical practice. Their coverage, major clinical trials, and potential

scenarios for utilization in clinical practice will be discussed in detail. A review of the major phase III clinical trial data can be seen in Table 3 for many of the agents discussed. Additionally, a review of the spectrum of activity for most agents can be seen in Table 4.

Table 3. Phase III trials of New Antimicrobial Agents.

Drug	Trial Name	Intervention	Source of Infection	Primary Endpoint	Results	Conclusion
CEF-TANI	CERTAIN-1	CEF-TANI (2 g + 0.5 g) or meropenem (1 g) q8h	cUTI	Microbiologic and clinical success on trial days 19 to 23 in the microITT population	70.6% in the CEF-TANI group and 58.0% in the meropenem group (treatment difference, 12.6 percentage points; 95% CI, 3.1 to 22.2; $p = 0.009$)	CEF-TANI was superior to meropenem for the treatment of cUTI
CEF-TANI	CERTAIN-2	CEF-TANI (2 g + 0.5 g) or meropenem (1 g) q8h	HAP/VAP	28-day all-cause mortality in the ITT population	Pending	Pending
CEF-EM	ALLIUM	CEF-EM (2 g + 0.5 g) or 4.5 g piperacillin-tazobactam q8h	cUTI or AP	Overall treatment success (clinical cure combined with microbiological eradication of infection)	79.1% in the CEF-EM group and 58.9% in the piperacillin-tazobactam group, (treatment difference, 21.2 percentage points; 95% CI, 14.3 to 27.9)	CEF-EM was non-inferior to piperacillin-tazobactam for the treatment of cUTI or AP
CEF-ZIDE	NCT04979806	CEF-ZIDE 3 g (2 g + 1 g) q8h or meropenem 1 g q8h	cUTI or AP	TOC for cUTI or AP at day 17 +/- 2 days	Pending	Pending
SUL-DUR	ATTACK	SUL-DUR (1 g each component) q6h or colistin 2.5 mg/kg q12h All patients received imipenem-cilastatin 1 g each component q6h	HAP/VAP, or BSI	28-day all-cause mortality the mMITT population NI margin was set at upper bound 95% CI of less than 20%	19% in the sul-dur group and 32% in the colistin group, (treatment difference of -13.2 percentage points; 95% CI, -30.0 to 3.5)	SUL-DUR was non-inferior to colistin, when each are given in combination with imipenem-cilastatin for the treatment of HAP, VAP, or BSI
Sulopenem	SURE 1	Sulopenem 500 mg/probenecid 500 mg PO twice daily for 5 days or ciprofloxacin 250 mg PO twice daily	Uncomplicated UTI	Combined clinical and microbiological response at day 12 in the mMITT population	65.6% in the sulopenem group and 67.9% in the ciprofloxacin group, (treatment difference -2.3 percentage points; 95% CI, -7.9 to 3.3)	Sulopenem was non-inferior to ciprofloxacin for the treatment of uncomplicated UTI
	SURE 2	Sulopenem 1000 mg IV once daily followed by oral sulopenem 500 mg/probenecid 500 mg or ertapenem 1000 mg IV once daily followed by oral ciprofloxacin 500 mg or amox/clav 875 mg twice daily	cUTI	Composite clinical and microbiologic outcomes at TOC in the mMITT population	67.8% in the sulopenem group and 73.9% in the ertapenem group, (treatment difference of -6.1 percentage points; 95% CI, -12 to -0.1)	Non-inferiority was not achieved by the sulopenem group for the treatment of cUTI

Table 3. Cont.

Drug	Trial Name	Intervention	Source of Infection	Primary Endpoint	Results	Conclusion
AZT-AVI	REVISIT	AZT-AVI (loading, extended loading and maintenance doses) ± MTZ 500 mg IV q 8 h vs. meropenem 1 g q 8 h ± colistin 9 million IU IV loading dose, followed by 9 million IU given IV daily in 2 or 3 divided doses	cIAI or HAP/VAP due to Gram-negative bacteria, including MBL-producing organisms	Clinical cure at TOC visit in ITT and clinically evaluable analysis sets	ITT: 68.4% in the AZT-AVI ± MTZ group and 65.7% in the meropenem ± colistin Clinically evaluable analysis set: 77% in the AZT-AVI ± MTZ group and 74.3% in the meropenem ± colistin group	AZT-AVI ± MTZ displayed similar efficacy compared to meropenem ± colistin for the treatment of cIAI and HAP/VAP
	ASSEMBLE	AZT-AVI (loading, extended loading and maintenance doses) ± MTZ 500 mg IV q 8 h or BAT	cIAI, HAP/VAP, cUTI or BSI with MBL Gram-negative bacteria isolated within 7 days prior to screening	Clinical cure at TOC in Micro-ITT analysis set at day 28	41.7% in the AZT-AVI ± MTZ group and 0% in the BAT group	Enrollment terminated early due to limited numbers of MBL associated infections (n = 15), no conclusions drawn from study results

Abbreviations: Amox/clav (amoxicillin/clavulanic acid); AP (acute pyelonephritis); AZT-AVI (Aztreonam-avibactam); BAT (best available therapy); BSI (bloodstream infection); CEM-EM (cefepime-enmetazobactam); CEF-TANI (cefepime-taniboractam); CEF-ZIDE (cefepime-zidebactam); CI (confidence interval); cIAI (complicated intra-abdominal infection); cUTI (complicated urinary tract infection); HAP (hospital-acquired pneumonia); ITT (intention-to-treat); IU (international units); IV (intravenous); MBL (metallo-β-lactamase); Micro-ITT (microbiology intention-to-treat); MITT (modified intention-to-treat); mMITT (microbiologically modified intention-to-treat); MTZ (metronidazole); NI (non-inferiority); PO (by mouth); q (every); qh (every hour); SUL-DUR (sulbactam-durlobactam); TOC (test-of-cure); UTI (urinary tract infection); VAP (ventilator-associated pneumonia).

Table 4. Spectrum of Activity.

Ambler Class	CEF-TANI	CEF-EM	CEF-ZIDE	SUL-DUR	Sulopenem	AZT-AVI
Class A:						
CTX-M	✓	✓	✓	✓	✓	✓
KPC	✓	✓	✓	✓	—	✓
Class B:						
NDM	✓	—	✓	—	—	✓
VIM	✓	—	✓	—	—	✓
IMP	—	—	✓	—	—	✓
Class C:						
AmpC	✓	✓	✓	✓	✓	✓
Class D:						
OXA-48	✓	✓	✓	✓	—	✓
Pathogens of Interest						
CRE	✓	✓	✓	—	—	✓
DTR	✓	✓	✓	—	—	✓
Pseudomonas CRAB	—	—	—	✓	—	—
Stenotrophomonas	—	—	—	—	—	✓

Abbreviations: AZT-AVI (Aztreonam-avibactam); CEF-EM (cefepime-enmetazobactam); CEF-TANI (cefepime-taniboractam); CEF-ZIDE (cefepime-zidebactam); CRAB (carbapenem-resistant *Acinetobacter baumannii*); CRE (carbapenem-resistant *Enterobacterales*); CTX-M (cefotaxime-hydrolyzing beta-lactamase isolated in Munich), DTR (difficult-to-treat resistance); IMP (active on imipenem) (imipenem-hydrolyzing beta-lactamase); KPC (*Klebsiella pneumoniae* carbapenemase); NDM (New Delhi metallo-beta-lactamase); OXA (oxacillinase), SUL-DUR (sulbactam-durlobactam); VIM (Verona integron-encoded metal-beta-lactamase).

4.1. Cefepime-Taniborbactam

Taniborbactam is a boric acid beta-lactamase inhibitor (BLI) that is structurally similar to vaborbactam but has a wider spectrum of inhibition due to enhanced pharmacokinetic (PK) parameters and unique side chain structure compared to vaborbactam [160]. Taniborbactam, unlike avibactam, has in vitro activity against all four Ambler classes of beta-lactamases, making it one of the broadest Gram-negative covering BLI to date [80,160,161]. Specifically, taniborbactam provides coverage against ESBL, CRE, MDR Pseudomonas, and MBL-producing pathogens, making taniborbactam one of the few BLI with activity against Ambler class B enzymes [80,160–164].

In 2024, Wagenlehner et al. published a phase III clinical trial (CERTAIN-1) evaluating the efficacy and safety of cefepime-taniborbactam in the treatment of complicated urinary tract infections (cUTIs) [165]. This trial demonstrated both non-inferiority and superiority of cefepime-taniborbactam compared to meropenem in terms of clinical cure rates and microbiological eradication of pathogens. Additionally, cefepime-taniborbactam had a favorable safety profile, with adverse events comparable to those observed with other antibiotics.

Cefepime-taniborbactam is a promising therapeutic option for the treatment of MDR Gram-negative bacterial infections. With favorable PK and pharmacodynamic (PD) characteristics, a well-defined dosing regimen, and demonstrated efficacy and safety in phase III clinical trials, cefepime-taniborbactam holds great promise for addressing the growing threat of antibiotic resistance in healthcare settings [166,167]. However, potential heteroresistance is a concern. In 2023, Abbott et al. highlighted a high occurrence of heteroresistance to cefepime-taniborbactam in 34 MBL-producing *Enterobacteriaceae* isolates [168]. This finding was concerning on two fronts. One, heteroresistance is difficult to detect with traditional AST, and two, heteroresistance is likely more widespread than initially believed and may contribute to “induced” selection of cefepime-taniborbactam resistance. Nonetheless, the broad Gram-negative coverage of cefepime-taniborbactam is highly appealing, particularly in locations with a high prevalence of a specific MBL, the New Delhi MBL (NDM).

In February 2024, the FDA rejected the new drug application (NDA) for cefepime-taniborbactam citing the need for additional manufacturing information. With an unknown timeline for approval, the race for the first FDA-approved beta-lactam-BLI combination to cover all four Ambler class enzymes continues.

4.2. Cefepime-Enmetazobactam

Enmetazobactam is a novel penicillanic acid sulfone BLI similar to the BLI tazobactam. The difference is the addition of a methyl group to the triazole moiety making enmetazobactam an extended-spectrum BLI with the ability to increase the potency of cefepime and restore its activity against Ambler Classes A, C, and D [169]. Further analysis of the in vitro activity of cefepime-enmetazobactam revealed that its activity against Ambler Classes C and D only seemed to improve when *Enterobacterales* isolates co-produced ESBLs [170]. This suggested that the expression of Class C and D beta-lactamases was severely downregulated by the ESBL gene, resulting in the phenotypic appearance of an ESBL alone.

The phase III, randomized, double-blind, active controlled trial (ALLIUM) evaluated the efficacy of cefepime-enmetazobactam for the treatment of cUTIs or acute pyelonephritis in adult patients. Patients were randomized to either cefepime-enmetazobactam or piperacillin-tazobactam for up to 14 days. Results from the study determined that among patients with cUTI or acute pyelonephritis caused by Gram-negative pathogens, cefepime-enmetazobactam was superior to piperacillin/tazobactam with respect to both clinical cure and microbiological eradication [171]. Additionally, cefepime-enmetazobactam was found to be highly tolerable among patients.

Cefepime-enmetazobactam was manufactured to serve as a carbapenem-sparing agent against organisms harboring ESBLs [172]. With cost being a driving factor for many hospital systems, especially those with limited formularies, along with the fact that cefepime-enmetazobactam offers little coverage against MBL and CRE pathogens, it is difficult

to imagine a clinical scenario where ceftazidime-avibactam will be preferred over current therapeutic options, at least initially. Despite this, ceftazidime-avibactam is an alternative treatment for pathogens co-producing both ESBL and OXA-48.

In February 2024, the FDA approved the usage of ceftazidime-avibactam for cUTI in adults based off the data from the ALLIUM trial.

4.3. Ceftazidime-Avibactam

Avibactam belongs to the bicyclo-acyl-hydrazide class of beta-lactam enhancers, which is a derivative and a newer generation of the diazabicyclooctane (DBO) BLIs [173,174]. These newer generation DBO are considered dual-acting beta-lactam inhibitors and enhancers due to their ability to inhibit penicillin binding proteins (PBPs), enhancing the activity of an associated beta-lactam antibiotic that works on different PBPs, while also inhibiting activity against serine class A, C, and D beta-lactamases [173–175]. Avibactam is a non-beta-lactam and thus, is not degraded by beta-lactamases. It has enhanced PBP2 binding in Gram-negative organisms, including *P. aeruginosa* and *A. baumannii*, and its enhancer effect is most demonstrated when combined with an agent targeted against PBP3 (i.e., ceftazidime) [173,176]. Ceftazidime-avibactam has demonstrated in vitro activity against carbapenem-resistant *Enterobacterales*, *P. aeruginosa*, and some *A. baumannii*. Avibactam alone has no activity against MBLs; however, when combined with ceftazidime, studies have demonstrated strong in vitro activity against these organisms [175,177–180]. Additionally, potential resistance mechanisms against ceftazidime-avibactam are not fully described. However, based on in vitro data among the *Enterobacterales*, *K. pneumoniae* ST14 co-producing NDM and OXA-48-type carbapenemases were often found to be resistant. For *P. aeruginosa*, in vitro data suggest that resistance may be due to overexpression of efflux pumps; however, the extent of efflux pump activity was more pronounced with ceftazidime alone vs. in combination with avibactam suggesting that avibactam is not readily effluxed [176].

A phase III, non-inferiority clinical trial (NCT04979806) is currently underway evaluating the clinical efficacy and safety of ceftazidime-avibactam for the treatment of cUTIs and pyelonephritis compared to meropenem. Until results of this trial are released, it is difficult to speculate about the potential role of avibactam in clinical practice. However, the combination of ceftazidime and avibactam has demonstrated activity against carbapenem-resistant Gram-negative organisms and is a potential option in the setting of MDR Gram-negative infections. Most notably, there have been two case reports highlighting the successful compassionate use of ceftazidime-avibactam. In both case reports, ceftazidime-avibactam was used as salvage therapy against NDM-producing *P. aeruginosa* in the setting of intra-abdominal infection and disseminated infection complicated by necrotizing ecthyma gangrenosum and respiratory infection [181,182].

4.4. Sulopenem

Like all beta-lactam antibiotics, sulopenem inhibits cell wall synthesis through binding to PBPs and inhibiting the final transpeptidation step of peptidoglycan synthesis. Specifically, sulopenem binds to the following PBPs with an order for affinity being greatest to least: PBP2, PBP1A, PBP1B, PBP4, PBP3, and PBP5 or 6 [183,184]. Structurally, sulopenem shares similarities and is often confused with carbapenems; however, carbapenems contain a proline ring while penems contain a thiazolidine ring that produces a smaller bond angle, reducing stress on the beta-lactam ring, and protects against enzymatic degradation. Sulopenem has been shown to have in vitro activity against ESBL and AmpC-producing *Enterobacterales* [185]. Additionally, its Gram-positive and anaerobic activity seems to mimic other carbapenems such as meropenem and imipenem, including minimal activity against *Enterococcus faecalis* [186]. Sulopenem is unaffected by many beta-lactamases with a few exceptions. MBLs and carbapenemase-producing organisms are resistant to sulopenem. Furthermore, sulopenem is ineffective against other resistance mechanisms such as efflux pumps and porin channel changes [187].

Sulopenem has been developed in both intravenous and oral formulations. The PK properties of intravenous sulopenem are similar to that of other carbapenems. Early studies showed that the oral prodrug formulation of sulopenem had variable bioavailability ranging from 20–34% [188]. Further studies revealed that bioavailability increases by 23.6% when given with food alone and up to 62% when administered with food and 500 mg of probenecid. It was noted that the effects of probenecid on bioavailability were greater when given with food. There was a difference of a 7.3% increase when sulopenem/probenecid were given alone and a 40.7% increase when both medications were given in combination with food [189].

Two major trials for sulopenem have been completed to date. The first trial, SURE-1, evaluated sulopenem as a treatment option for uncomplicated UTIs caused by Gram-negative bacteria [190,191]. In the second trial, SURE-2, evaluated sulopenem as a treatment option for cUTIs and acute pyelonephritis caused by Gram-negative bacteria [192,193]. The results of these trials demonstrated that sulopenem was non-inferior to standard antibiotics in treating both uncomplicated and complicated UTIs, indicating its potential as an alternative treatment option. In addition, sulopenem demonstrated a favorable safety profile with few adverse effects reported, including no increases in the incidence of *Clostridioides difficile* (*C. difficile*) colitis.

4.5. Aztreonam-Avibactam

Aztreonam is a monobactam, working similarly to others in its class by binding to PBPs and inhibiting cell wall synthesis. Aztreonam can withstand hydrolyzation from MBLs, unlike other beta-lactam antibiotics. Despite its activity against MBL producers, these isolates often co-produce serine-beta-lactamases (AmpC beta-lactamases, ESBLs, and KPCs) which can hydrolyze it. Avibactam is a DBO non-beta-lactam BLI with activity against Ambler class A, C, and some class D beta-lactamases [194]. In combination with avibactam, the degradation of aztreonam is prevented as the avibactam component inhibits these co-produced beta-lactamase enzymes. Previous studies have cited the combination of CTZ-AVI and aztreonam as a treatment option for serious infections involving MBL producers [195,196]. Therefore, a combination product of aztreonam-avibactam proves to be a promising antimicrobial agent. Aztreonam/avibactam's spectrum activity includes coverage against carbapenemase-producing *Enterobacterales* including those producing KPCs, VIM, IMP, NDM, and OXA-48. Additionally, the combination has activity against *Pseudomonas aeruginosa* and *S. maltophilia*. Aztreonam/avibactam lacks activity against *A. baumannii* due to OXA-type enzymes [197–199]. Pseudomonal resistance to aztreonam/avibactam has been attributed to production of *Pseudomonas*-derived cephalosporinase 1 (PDC), OXA enzymes (not including OXA-48), loss of porins, and overexpression of efflux pumps [197]. Resistance to *Enterobacterales* is suspected to be attributed to amino acid insertion in the PBP3 determinants, reducing aztreonam's ability to bind [197].

The phase IIa open-label, multicenter study REJUVENATE studied the PK profile, safety, and efficacy of aztreonam/avibactam in patients with complicated intra-abdominal infections (cIAIs). The study supported the use of aztreonam/avibactam 500/167 mg loading dose infused over 30 min followed by 1500/500 mg every six hours maintenance regimen with doses infused over three hours. Dosing was determined for patients with an estimated creatinine clearance > 50 mL/min [200]. The REJUVENATE trial cited the most common adverse reaction to be an increase in hepatic enzymes, occurring in 26.5% of patients, most of which were asymptomatic and recovered upon discontinuation of treatment. Diarrhea was listed as the second most common adverse event, but none associated with *C. difficile* [200].

In clinical practice, aztreonam-avibactam holds promise as a combination therapy with coverage against all four Ambler beta-lactamase classes. Specifically, this combination may prove to be useful in combating pathogens co-harboring both MBL and class A/D enzymes.

4.6. Sulbactam-Durlobactam

Sulbactam is a well-known BLI with antibacterial activity against *A. baumannii* [23,201,202]. However, resistance to ampicillin/sulbactam is growing, leaving a major coverage gap in clinical practice for CRAB [17,203–205]. To combat this, sulbactam was commercially launched with durlobactam, which is a DBO BLI with activity against class A, C, and D beta-lactamases [206–208]. With structural similarities to avibactam, its endocyclic double bond and methyl substituent enhance the potency of durlobactam as a BLI and allow the inhibition of a wide range of Class D beta-lactamases commonly produced by *A. baumannii* [209]. Of note, durlobactam has been reported to have intrinsic activity against some species of *Enterobacteriaceae* through inhibition of PBP2, but it does not have intrinsic activity against *A. baumannii* when given on its own; however, both in vivo and in vitro activity have been achieved when given in combination with sulbactam [210,211].

In 2023, the ATTACK trial was published evaluating the usage of sulbactam-durlobactam in patients with either hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and/or bacteremia caused by *Acinetobacter baumannii-calcoaceticus* complex (ABC). Sulbactam-durlobactam was compared to colistin, and all patients received imipenem-cilastatin as background therapy. Results from this trial demonstrated that sulbactam-durlobactam was non-inferior to colistin for the primary endpoint of all-cause 28-day mortality. Additionally, sulbactam-durlobactam was less nephrotoxic compared to colistin [206].

Results from the ATTACK trial led to the FDA approval of sulbactam-durlobactam for HAP/VAP caused by susceptible isolates of ABC in 2023. Given the rise in incidence of CRAB cases in the U.S., sulbactam/durlobactam has potential for use in other MDR CRAB infections outside of the respiratory tract, including those resistant to other salvage therapy options [212].

5. Other BLI/BL/BLI Combinations

5.1. Xeruborbactam

Xeruborbactam (QPX7728) is a cyclic boronate inhibitor that is active against all four Ambler beta-lactamase classes. Xeruborbactam has shown in vitro activity against MBL isolates not inhibited by taniborbactam, specifically IMP and NDM-9 [213–215]. Additionally, xeruborbactam has demonstrated the ability, in vitro, to recover meropenem susceptibilities [213,215,216]. In a study by Lomovskaya et al., xeruborbactam was able to increase potency against meropenem-resistant KPC-producing strains of *K. pneumoniae*, NDM-1-producing strain of *E. coli*, and VIM-1-producing strain of *K. pneumoniae* [214]. Together, these results suggest xeruborbactam may have a role as both a recovery agent for certain beta-lactam antibiotics and a treatment option for MBL-producing bacteria.

Current phase III studies are lacking for xeruborbactam. However, multiple phase I trials have been completed. These trials demonstrated a favorable safety and PK profile for xeruborbactam [217,218]. Additional clinical data are needed to determine the role of xeruborbactam in clinical practice, but in vitro data favor further exploration of xeruborbactam.

5.2. Nacubactam

Nacubactam (OP0595, RG6080) is a DBO BLI with a distinctive dual mechanism of action compared to its sister compound avibactam [219–221]. It demonstrates activity against a broad spectrum of beta-lactamases, including class A, C, and some class D enzymes. Additionally, nacubactam is also an inhibitor of PBP2 in the cell wall of *Enterobacteriaceae*, which enhances the activity of co-administered beta-lactams. Together, this broad spectrum of activity suggests potential efficacy against a wide range of MDR bacteria, including those producing ESBLs and CRE [219–222].

While there is limited published clinical trial data available, there are ongoing studies evaluating the efficacy and safety of nacubactam in combination with various beta-lactam antibiotics. A phase II trial published in *Clinical Infectious Diseases* in 2020, evaluated the efficacy of nacubactam in combination with meropenem for the treatment of cUTIs and

cIAIs caused by CRE [219]. The results demonstrated favorable clinical outcomes and tolerability, suggesting the potential utility of nacubactam in this patient population. Two other phase III trials are actively recruiting to evaluate the efficacy of cefepime-nacubactam and aztreonam-nacubactam for cUTIs and infections involving CRE (Integral-1 and Integral-2 trials).

6. Conclusions

In 1928, Alexander Fleming discovered that *Penicillium notatum* inhibited *Staphylococcus* spp. within a Petri dish, and by the early 1950s, penicillin became a mainstay of treatment for numerous infections [223,224]. Unfortunately, upon its utilization in clinical practice, a biological time clock started for the global dispersion of penicillin-resistant pathogens. Fast-forward to today, and that same biological clock continues to tick for antibiotics deployed in clinical practice. Traditionally, researchers and clinicians have strived for the development of newer antimicrobial agents that have the potential to overcome emerging resistant mechanisms of commonly encountered pathogens, but this retrospective approach is not sustainable [146,225,226]. As AMR continues to emerge, and few novel antibiotics are on the horizon, the focus must shift to preventive measures to slow the spread of resistant pathogens [227–229]. These measures should consist of a combination of standardized AMS programs that are adequately funded, guideline and culture-driven antibiotic prescribing practices, especially in the outpatient setting, properly funded global health programs, and strict infection prevention policies that focus on the importance of hand hygiene and personal protective equipment [8,93,227,229–232]. Ultimately, without drastic changes in healthcare reimbursement, global awareness of AMR, and antibiotic research drug development, preventive and supportive measures will become the standard of practice for infections caused by resistant bacterial pathogens that were once susceptible to employed antibiotics. This generated environment will likely become the largest global pandemic in modern time.

Author Contributions: Conceptualization, J.M.K., A.V., J.S., R.F. and C.W.; writing—original draft preparation, J.M.K., A.V., J.S., R.F. and C.W.; writing—review and editing, J.M.K., A.V., J.S., R.F., C.W., M.P. and M.M.; visualization, J.M.K., A.V., M.P. and M.M.; supervision, J.M.K.; project administration, J.M.K. and A.V. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This study did not meet the qualifications for IRB submission at University of Arkansas for Medical Sciences.

Data Availability Statement: Not applicable.

Conflicts of Interest: J. Myles Keck is a speaker representative for AbbVie (Avycaz and Cefiderocol). The remaining authors declare no conflicts of interest.

References

- Centers for Disease Control and Prevention. *Antibiotic Resistance Threats in the United States, 2019*; Centers for Disease Control and Prevention: Atlanta, GA, USA, 2019.
- Terreni, M.; Taccani, M.; Pregnolato, M. New Antibiotics for Multidrug-Resistant Bacterial Strains: Latest Research Developments and Future Perspectives. *Molecules* **2021**, *26*, 2671. [[CrossRef](#)]
- Shi, Z.; Zhang, J.; Tian, L.; Xin, L.; Liang, C.; Ren, X.; Li, M. A Comprehensive Overview of the Antibiotics Approved in the Last Two Decades: Retrospects and Prospects. *Molecules* **2023**, *28*, 1762. [[CrossRef](#)]
- Walsh, T.R.; Gales, A.C.; Laxminarayan, R.; Dodd, P.C. Antimicrobial Resistance: Addressing a Global Threat to Humanity. *PLoS Med.* **2023**, *20*, e1004264. [[CrossRef](#)] [[PubMed](#)]
- Suay-García, B.; Pérez-Gracia, M.T. Present and Future of Carbapenem-resistant Enterobacteriaceae (CRE) Infections. *Antibiotics* **2019**, *8*, 122. [[CrossRef](#)] [[PubMed](#)]
- Dequin, P.-F.; Aubron, C.; Faure, H.; Garot, D.; Guillot, M.; Hamzaoui, O.; Lemiale, V.; Maizel, J.; Mootien, J.Y.; Osman, D.; et al. The place of new antibiotics for Gram-negative bacterial infections in intensive care: Report of a consensus conference. *Ann. Intensive Care* **2023**, *13*, 59. [[CrossRef](#)]

7. Hwang, S.; Kwon, K.T. Core Elements for Successful Implementation of Antimicrobial Stewardship Programs. *Infect. Chemother.* **2021**, *53*, 421–435. [[CrossRef](#)]
8. Pollack, L.A.; Srinivasan, A. Core Elements of Hospital Antibiotic Stewardship Programs From the Centers for Disease Control and Prevention. *Clin. Infect. Dis.* **2014**, *59*, S97–S100. [[CrossRef](#)] [[PubMed](#)]
9. Centers for Disease Control and Prevention. *Core Elements of Hospital Antibiotic Stewardship Programs*; Centers for Disease Control and Prevention: Atlanta, GA, USA, 2014.
10. Theuretzbacher, U. Global antimicrobial resistance in Gram-negative pathogens and clinical need. *Curr. Opin. Microbiol.* **2017**, *39*, 106–112. [[CrossRef](#)]
11. Aljeldah, M.M. Antimicrobial Resistance and Its Spread Is a Global Threat. *Antibiotics* **2022**, *11*, 1082. [[CrossRef](#)]
12. Bassetti, M.; Kanj, S.S.; Kiratisin, P.; Rodrigues, C.; Van Duin, D.; Villegas, M.V.; Yu, Y. Early appropriate diagnostics and treatment of MDR Gram-negative infections. *JAC-Antimicrob. Resist.* **2022**, *4*, dlac089. [[CrossRef](#)]
13. Shanmugakani, R.K.; Srinivasan, B.; Glesby, M.J.; Westblade, L.F.; Cárdenas, W.B.; Raj, T.; Erickson, D.; Mehta, S. Current state of the art in rapid diagnostics for antimicrobial resistance. *Lab A Chip* **2020**, *20*, 2607–2625. [[CrossRef](#)] [[PubMed](#)]
14. Ryu, H.; Abdul Azim, A.; Bhatt, P.J.; Uprety, P.; Mohayya, S.; Dixit, D.; Kirn, T.J.; Narayanan, N. Rapid Diagnostics to Enhance Therapy Selection for the Treatment of Bacterial Infections. *Curr. Pharmacol. Rep.* **2023**, *9*, 198–216. [[CrossRef](#)]
15. Gupta, E.; Saxena, J.; Kumar, S.; Sharma, U.; Rastogi, S.; Srivastava, V.K.; Kaushik, S.; Jyoti, A. Fast Track Diagnostic Tools for Clinical Management of Sepsis: Paradigm Shift from Conventional to Advanced Methods. *Diagnostics* **2023**, *13*, 277. [[CrossRef](#)] [[PubMed](#)]
16. Kaprou, G.D.; Bergšpica, I.; Alexa, E.A.; Alvarez-Ordóñez, A.; Prieto, M. Rapid Methods for Antimicrobial Resistance Diagnostics. *Antibiotics* **2021**, *10*, 209. [[CrossRef](#)] [[PubMed](#)]
17. Murray, C.J.L.; Ikuta, K.S.; Sharara, F.; Swetschinski, L.; Robles Aguilar, G.; Gray, A.; Han, C.; Bisignano, C.; Rao, P.; Wool, E.; et al. Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis. *Lancet* **2022**, *399*, 629–655. [[CrossRef](#)] [[PubMed](#)]
18. Russell, P.S. *Clinical Approach to Infection in the Compromised Host*; Springer: Berlin/Heidelberg, Germany, 2013.
19. Bosso, J.A.; Mauldin, P.D.; Salgado, C.D. The association between antibiotic use and resistance: The role of secondary antibiotics. *Eur. J. Clin. Microbiol. Infect. Dis.* **2010**, *29*, 1125–1129. [[CrossRef](#)]
20. Jean, S.-S.; Liu, I.M.; Hsieh, P.-C.; Kuo, D.-H.; Liu, Y.-L.; Hsueh, P.-R. Off-label use versus formal recommendations of conventional and novel antibiotics for the treatment of infections caused by multidrug-resistant bacteria. *Int. J. Antimicrob. Agents* **2023**, *61*, 106763. [[CrossRef](#)] [[PubMed](#)]
21. Bassetti, M.; Peghin, M.; Vena, A.; Giacobbe, D.R. Treatment of Infections Due to MDR Gram-Negative Bacteria. *Front. Med.* **2019**, *6*, 74. [[CrossRef](#)] [[PubMed](#)]
22. Corona, A.; De Santis, V.; Agarossi, A.; Prete, A.; Cattaneo, D.; Tomasini, G.; Bonetti, G.; Patroni, A.; Latronico, N. Antibiotic Therapy Strategies for Treating Gram-Negative Severe Infections in the Critically Ill: A Narrative Review. *Antibiotics* **2023**, *12*, 1262. [[CrossRef](#)]
23. Tamma, P.D.; Aitken, S.L.; Bonomo, R.A.; Mathers, A.J.; van Duin, D.; Clancy, C.J. Infectious Diseases Society of America 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections. *Clin. Infect. Dis.* **2023**, ciad428. [[CrossRef](#)]
24. Eubank, T.A.; Long, S.W.; Perez, K.K. Role of Rapid Diagnostics in Diagnosis and Management of Patients with Sepsis. *J. Infect. Dis.* **2020**, *222*, S103–S109. [[CrossRef](#)] [[PubMed](#)]
25. Van Heuverswyn, J.; Valik, J.K.; Desirée van der Werff, S.; Hedberg, P.; Giske, C.; Naucmér, P. Association Between Time to Appropriate Antimicrobial Treatment and 30-day Mortality in Patients with Bloodstream Infections: A Retrospective Cohort Study. *Clin. Infect. Dis.* **2023**, *76*, 469–478. [[CrossRef](#)] [[PubMed](#)]
26. Hassall, J.; Coxon, C.; Patel, V.C.; Goldenberg, S.D.; Sergaki, C. Limitations of current techniques in clinical antimicrobial resistance diagnosis: Examples and future prospects. *npj Antimicrob. Resist.* **2024**, *2*, 16. [[CrossRef](#)]
27. Zasowski, E.J.; Bassetti, M.; Blasi, F.; Goossens, H.; Rello, J.; Sotgiu, G.; Tavoschi, L.; Arber, M.R.; McCool, R.; Patterson, J.V.; et al. A Systematic Review of the Effect of Delayed Appropriate Antibiotic Treatment on the Outcomes of Patients with Severe Bacterial Infections. *Chest* **2020**, *158*, 929–938. [[CrossRef](#)] [[PubMed](#)]
28. Wenzler, E.; Maximos, M.; Asempa, T.E.; Biehle, L.; Schuetz, A.N.; Hirsch, E.B. Antimicrobial susceptibility testing: An updated primer for clinicians in the era of antimicrobial resistance: Insights from the Society of Infectious Diseases Pharmacists. *Pharmacother. J. Hum. Pharmacol. Drug Ther.* **2023**, *43*, 264–278. [[CrossRef](#)] [[PubMed](#)]
29. Schinas, G.; Dimopoulos, G.; Akinosoglou, K. Understanding and Implementing Diagnostic Stewardship: A Guide for Resident Physicians in the Era of Antimicrobial Resistance. *Microorganisms* **2023**, *11*, 2214. [[CrossRef](#)] [[PubMed](#)]
30. Filice, G.A.; Drekonja, D.M.; Thurn, J.R.; Hamann, G.M.; Masoud, B.T.; Johnson, J.R. Diagnostic Errors that Lead to Inappropriate Antimicrobial Use. *Infect. Control. Hosp. Epidemiol.* **2015**, *36*, 949–956. [[CrossRef](#)] [[PubMed](#)]
31. Curren, E.J.; Lutgring, J.D.; Kabbani, S.; Diekema, D.J.; Gitterman, S.; Lautenbach, E.; Morgan, D.J.; Rock, C.; Salerno, R.M.; McDonald, L.C. Advancing Diagnostic Stewardship for Healthcare-Associated Infections, Antibiotic Resistance, and Sepsis. *Clin. Infect. Dis.* **2021**, *74*, 723–728. [[CrossRef](#)]
32. Haddad, M.; Sheybani, F.; Naderi, H.; Sasan, M.S.; Najaf Najafi, M.; Sedighi, M.; Seddigh, A. Errors in Diagnosing Infectious Diseases: A Physician Survey. *Front. Med.* **2021**, *8*, 779454. [[CrossRef](#)]
33. Gniadkowski, M. Evolution and epidemiology of extended-spectrum β -lactamases (ESBLs) and ESBL-producing microorganisms. *Clin. Microbiol. Infect.* **2001**, *7*, 597–608. [[CrossRef](#)]

34. Pitout, J.D.; Nordmann, P.; Laupland, K.B.; Poirel, L. Emergence of Enterobacteriaceae producing extended-spectrum beta-lactamases (ESBLs) in the community. *J. Antimicrob. Chemother.* **2005**, *56*, 52–59. [[CrossRef](#)] [[PubMed](#)]
35. Raphael, E.; Glymour, M.M.; Chambers, H.F. Trends in prevalence of extended-spectrum beta-lactamase-producing *Escherichia coli* isolated from patients with community- and healthcare-associated bacteriuria: Results from 2014 to 2020 in an urban safety-net healthcare system. *Antimicrob. Resist. Infect. Control* **2021**, *10*, 118. [[CrossRef](#)] [[PubMed](#)]
36. 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*, 254–259. [[CrossRef](#)] [[PubMed](#)]
37. Handal, N.; Whitworth, J.; Lyngbakken, M.N.; Berdal, J.E.; Dalgard, O.; Bakken Jørgensen, S. Mortality and length of hospital stay after bloodstream infections caused by ESBL-producing compared to non-ESBL-producing *E. coli*. *Infect. Dis.* **2024**, *56*, 19–31. [[CrossRef](#)] [[PubMed](#)]
38. Lodise, T.P.; Berger, A.; Altincatal, A.; Wang, R.; Bhagnani, T.; Gillard, P.; Bonine, N.G. Antimicrobial Resistance or Delayed Appropriate Therapy—Does One Influence Outcomes More Than the Other Among Patients with Serious Infections Due to Carbapenem-Resistant versus Carbapenem-Susceptible Enterobacteriaceae? *Open Forum. Infect. Dis.* **2019**, *6*, ofz194. [[CrossRef](#)]
39. Barenfanger, J.; Drake, C.; Kacich, G. Clinical and Financial Benefits of Rapid Bacterial Identification and Antimicrobial Susceptibility Testing. *J. Clin. Microbiol.* **1999**, *37*, 1415–1418. [[CrossRef](#)] [[PubMed](#)]
40. Kerremans, J.J.; Verboom, P.; Stijnen, T.; Hakkaart-van Roijen, L.; Goessens, W.; Verbrugh, H.A.; Vos, M.C. Rapid identification and antimicrobial susceptibility testing reduce antibiotic use and accelerate pathogen-directed antibiotic use. *J. Antimicrob. Chemother.* **2007**, *61*, 428–435. [[CrossRef](#)] [[PubMed](#)]
41. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Global Health; Board on Health Sciences Policy; Forum on Drug Discovery, Development, and Translation; Forum on Medical and Public Health Preparedness for Disasters and Emergencies; Forum on Microbial Threats; Erin Hammers Forstag and Carolyn Shore, Rapporteurs. The National Academies Collection: Reports funded by National Institutes of Health. In *Accelerating the Development and Uptake of Rapid Diagnostics to Address Antibiotic Resistance: Proceedings of a Workshop*; Shore, C., Forstag, E.H., Eds.; National Academies Press (US): Washington, DC, USA, 2023. [[CrossRef](#)]
42. Medina, E.; Pieper, D.H. Tackling Threats and Future Problems of Multidrug-Resistant Bacteria. *Curr. Top. Microbiol. Immunol.* **2016**, *398*, 3–33. [[CrossRef](#)] [[PubMed](#)]
43. Jhaveri, T.A.; Weiss, Z.F.; Winkler, M.L.; Pyden, A.D.; Basu, S.S.; Pecora, N.D. A decade of clinical microbiology: Top 10 advances in 10 years: What every infection preventionist and antimicrobial steward should know. *Antimicrob. Steward. Healthc. Epidemiol.* **2024**, *4*, e8. [[CrossRef](#)]
44. Durante-Mangoni, E.; Andini, R.; Zampino, R. Management of carbapenem-resistant Enterobacteriaceae infections. *Clin. Microbiol. Infect.* **2019**, *25*, 943–950. [[CrossRef](#)]
45. Logan, L.K.; Weinstein, R.A. The Epidemiology of Carbapenem-Resistant Enterobacteriaceae: The Impact and Evolution of a Global Menace. *J. Infect. Dis.* **2017**, *215*, S28–S36. [[CrossRef](#)] [[PubMed](#)]
46. Strich, J.R.; Mishuk, A.; Diao, G.; Lawandi, A.; Li, W.; Demirkale, C.Y.; Babiker, A.; Mancera, A.; Swihart, B.J.; Walker, M.; et al. Assessing Clinician Utilization of Next-Generation Antibiotics against Resistant Gram-Negative Infections in U.S. Hospitals. *Ann. Intern. Med.* **2024**, *177*, 559–572. [[CrossRef](#)] [[PubMed](#)]
47. Gaibani, P.; Giani, T.; Bovo, F.; Lombardo, D.; Amadesi, S.; Lazzarotto, T.; Coppi, M.; Rossolini, G.M.; Ambretti, S. Resistance to Ceftazidime/Avibactam, Meropenem/Vaborbactam and Imipenem/Relebactam in Gram-Negative MDR Bacilli: Molecular Mechanisms and Susceptibility Testing. *Antibiotics* **2022**, *11*, 628. [[CrossRef](#)] [[PubMed](#)]
48. European Congress of Clinical Microbiology & Infectious Diseases. *Not Enough New Antibiotics in the Pipeline, Concludes WHO Review—Especially Those Targeting Deadly Drug-Resistant Microbes*; European Congress of Clinical Microbiology & Infectious Diseases: Basel, Switzerland, 2023.
49. Miller, E.; Sikes, H.D. Addressing Barriers to the Development and Adoption of Rapid Diagnostic Tests in Global Health. *Nanobiomedicine* **2015**, *2*, 6. [[CrossRef](#)] [[PubMed](#)]
50. Yimer, S.A.; Booij, B.B.; Tobert, G.; Hebbeler, A.; Oloo, P.; Brangel, P.; L’Azou Jackson, M.; Jarman, R.; Craig, D.; Avumegah, M.S.; et al. Rapid diagnostic test: A critical need for outbreak preparedness and response for high priority pathogens. *BMJ Glob. Health* **2024**, *9*, e014386. [[CrossRef](#)] [[PubMed](#)]
51. Trevas, D.; Caliendo, A.M.; Hanson, K.; Levy, J.; Ginocchio, C.C. Diagnostic Tests Can Stem the Threat of Antimicrobial Resistance: Infectious Disease Professionals Can Help. *Clin. Infect. Dis.* **2020**, *72*, e893–e900. [[CrossRef](#)] [[PubMed](#)]
52. Ferreyra, C.; Gleeson, B.; Kapon, O.; Mendelson, M. Diagnostic tests to mitigate the antimicrobial resistance pandemic—Still the problem child. *PLoS Glob. Public Health* **2022**, *2*, e0000710. [[CrossRef](#)] [[PubMed](#)]
53. Yip, A.Y.G.; King, O.G.; Omelchenko, O.; Kurkimat, S.; Horrocks, V.; Mostyn, P.; Danckert, N.; Ghani, R.; Satta, G.; Jauneikaite, E.; et al. Antibiotics promote intestinal growth of carbapenem-resistant Enterobacteriaceae by enriching nutrients and depleting microbial metabolites. *Nat. Commun.* **2023**, *14*, 5094. [[CrossRef](#)] [[PubMed](#)]
54. Ramirez, J.; Guarner, F.; Bustos Fernandez, L.; Maruy, A.; Sdepanian, V.L.; Cohen, H. Antibiotics as Major Disruptors of Gut Microbiota. *Front. Cell. Infect. Microbiol.* **2020**, *10*, 572912. [[CrossRef](#)]
55. Tan, S.Y.; Khan, R.A.; Khalid, K.E.; Chong, C.W.; Bakhtiar, A. Correlation between antibiotic consumption and the occurrence of multidrug-resistant organisms in a Malaysian tertiary hospital: A 3-year observational study. *Sci. Rep.* **2022**, *12*, 3106. [[CrossRef](#)]

56. Peeters, P.; Ryan, K.; Karve, S.; Potter, D.; Baelen, E.; Rojas-Farreras, S.; Rodríguez-Baño, J. The impact of initial antibiotic treatment failure: Real-world insights in patients with complicated, health care-associated intra-abdominal infection. *Infect. Drug Resist.* **2019**, *12*, 329–343. [[CrossRef](#)] [[PubMed](#)]
57. Ryan, K.; Karve, S.; Peeters, P.; Baelen, E.; Potter, D.; Rojas-Farreras, S.; Pascual, E.; Rodríguez-Baño, J. The impact of initial antibiotic treatment failure: Real-world insights in healthcare-associated or nosocomial pneumonia. *J. Infect.* **2018**, *77*, 9–17. [[CrossRef](#)] [[PubMed](#)]
58. Wu, H.-J.; Xiao, Z.-G.; Lv, X.-J.; Huang, H.-T.; Liao, C.; Hui, C.-Y.; Xu, Y.; Li, H.-F. Drug-resistant *Acinetobacter baumannii*: From molecular mechanisms to potential therapeutics (Review). *Exp. Ther. Med.* **2023**, *25*, 209. [[CrossRef](#)] [[PubMed](#)]
59. Barta, C.; Rolston, K.V.I.; Neshor, L. Carbapenem-resistant *Acinetobacter baumannii*: Colonization, Infection and Current Treatment Options. *Infect. Dis. Ther.* **2022**, *11*, 683–694. [[CrossRef](#)] [[PubMed](#)]
60. Shields, R.K.; Paterson, D.L.; Tamma, P.D. Navigating Available Treatment Options for Carbapenem-Resistant *Acinetobacter baumannii*-calcoaceticus Complex Infections. *Clin. Infect. Dis.* **2023**, *76*, S179–S193. [[CrossRef](#)] [[PubMed](#)]
61. Karruli, A.; Migliaccio, A.; Pournaras, S.; Durante-Mangoni, E.; Zarrilli, R. Cefiderocol and Sulbactam-Durlobactam against Carbapenem-Resistant *Acinetobacter baumannii*. *Antibiotics* **2023**, *12*, 1729. [[CrossRef](#)] [[PubMed](#)]
62. Nutman, A.; Temkin, E.; Lellouche, J.; Ben David, D.; Schwartz, D.; Carmeli, Y. Detecting carbapenem-resistant *Acinetobacter baumannii* (CRAB) carriage: Which body site should be cultured? *Infect. Control Hosp. Epidemiol.* **2020**, *41*, 965–967. [[CrossRef](#)] [[PubMed](#)]
63. Anwer, R. Molecular epidemiology and molecular typing methods of *Acinetobacter baumannii*: An updated review. *Saudi Med. J.* **2024**, *45*, 458–467. [[CrossRef](#)]
64. Ajao, A.O.; Robinson, G.; Lee, M.S.; Ranke, T.D.; Venezia, R.A.; Furuno, J.P.; Harris, A.D.; Johnson, J.K. Comparison of culture media for detection of *Acinetobacter baumannii* in surveillance cultures of critically-ill patients. *Eur. J. Clin. Microbiol. Infect. Dis.* **2011**, *30*, 1425–1430. [[CrossRef](#)]
65. Giacobbe, D.R.; Giani, T.; Bassetti, M.; Marchese, A.; Viscoli, C.; Rossolini, G.M. Rapid microbiological tests for bloodstream infections due to multidrug resistant Gram-negative bacteria: Therapeutic implications. *Clin. Microbiol. Infect.* **2020**, *26*, 713–722. [[CrossRef](#)]
66. Serapide, F.; Guastalegname, M.; Gulli, S.P.; Lionello, R.; Bruni, A.; Garofalo, E.; Longhini, F.; Trecarichi, E.M.; Russo, A. Antibiotic Treatment of Carbapenem-Resistant *Acinetobacter baumannii* Infections in View of the Newly Developed β -Lactams: A Narrative Review of the Existing Evidence. *Antibiotics* **2024**, *13*, 506. [[CrossRef](#)] [[PubMed](#)]
67. Huang, E.; Thompson, R.N.; Moon, S.H.; Keck, J.M.; Lowry, M.S.; Melero, J.; Jun, S.R.; Rosenbaum, E.R.; Dare, R.K. Treatment-emergent cefiderocol resistance in carbapenem-resistant *Acinetobacter baumannii* is associated with insertion sequence ISAb36 in the siderophore receptor *pirA*. *Antimicrob. Agents Chemother.* **2024**, *68*, e00290-24. [[CrossRef](#)]
68. Desmoulin, A.; Sababadichetty, L.; Kamus, L.; Daniel, M.; Feletti, L.; Allou, N.; Potron, A.; Leroy, A.-G.; Jaffar-Bandjee, M.-C.; Belmonte, O.; et al. Adaptive resistance to cefiderocol in carbapenem-resistant *Acinetobacter baumannii* (CRAB): Microbiological and clinical issues. *Heliyon* **2024**, *10*, e30365. [[CrossRef](#)]
69. Findlay, J.; Bianco, G.; Boattini, M.; Nordmann, P. In vivo development of cefiderocol resistance in carbapenem-resistant *Acinetobacter baumannii* associated with the downregulation of a TonB-dependent siderophore receptor, *PiuA*. *J. Antimicrob. Chemother.* **2024**, *79*, 928–930. [[CrossRef](#)] [[PubMed](#)]
70. Bassetti, M.; Echols, R.; Matsunaga, Y.; Ariyasu, M.; Doi, Y.; Ferrer, R.; Lodise, T.P.; Naas, T.; Niki, Y.; Paterson, D.L.; et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): A randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. *Lancet Infect. Dis.* **2021**, *21*, 226–240. [[CrossRef](#)] [[PubMed](#)]
71. Gatti, M.; Cosentino, F.; Giannella, M.; Viale, P.; Pea, F. Clinical efficacy of cefiderocol-based regimens in patients with carbapenem-resistant *Acinetobacter baumannii* infections: A systematic review with meta-analysis. *Int. J. Antimicrob. Agents* **2024**, *63*, 107047. [[CrossRef](#)]
72. Kollef, M.; Dupont, H.; Greenberg, D.E.; Viale, P.; Echols, R.; Yamano, Y.; Nicolau, D.P. Prospective role of cefiderocol in the management of carbapenem-resistant *Acinetobacter baumannii* infections: Review of the evidence. *Int. J. Antimicrob. Agents* **2023**, *62*, 106882. [[CrossRef](#)]
73. Wong, D.; Holtom, P.; Spellberg, B. Osteomyelitis Complicating Sacral Pressure Ulcers: Whether or Not to Treat with Antibiotic Therapy. *Clin. Infect. Dis.* **2019**, *68*, 338–342. [[CrossRef](#)]
74. Darby, E.M.; Trampari, E.; Siasat, P.; Gaya, M.S.; Alav, I.; Webber, M.A.; Blair, J.M.A. Molecular mechanisms of antibiotic resistance revisited. *Nat. Rev. Microbiol.* **2023**, *21*, 280–295. [[CrossRef](#)]
75. Peterson, E.; Kaur, P. Antibiotic Resistance Mechanisms in Bacteria: Relationships Between Resistance Determinants of Antibiotic Producers, Environmental Bacteria, and Clinical Pathogens. *Front. Microbiol.* **2018**, *9*, 2928. [[CrossRef](#)]
76. Zhang, F.; Cheng, W. The Mechanism of Bacterial Resistance and Potential Bacteriostatic Strategies. *Antibiotics* **2022**, *11*, 1215. [[CrossRef](#)] [[PubMed](#)]
77. Bush, K.; Jacoby, G.A. Updated functional classification of beta-lactamases. *Antimicrob. Agents Chemother.* **2010**, *54*, 969–976. [[CrossRef](#)] [[PubMed](#)]
78. Sawa, T.; Kooguchi, K.; Moriyama, K. Molecular diversity of extended-spectrum β -lactamases and carbapenemases, and antimicrobial resistance. *J. Intensive Care* **2020**, *8*, 13. [[CrossRef](#)] [[PubMed](#)]

79. Husna, A.; Rahman, M.M.; Badruzzaman, A.T.M.; Sikder, M.H.; Islam, M.R.; Rahman, M.T.; Alam, J.; Ashour, H.M. Extended-Spectrum β -Lactamases (ESBL): Challenges and Opportunities. *Biomedicines* **2023**, *11*, 2937. [[CrossRef](#)] [[PubMed](#)]
80. Bush, K.; Bradford, P.A. Interplay between β -lactamases and new β -lactamase inhibitors. *Nat. Rev. Microbiol.* **2019**, *17*, 295–306. [[CrossRef](#)] [[PubMed](#)]
81. Bush, K. Classification for β -lactamases: Historical perspectives. *Expert Rev. Anti-Infect. Ther.* **2023**, *21*, 513–522. [[CrossRef](#)] [[PubMed](#)]
82. Tooke, C.L.; Hinchliffe, P.; Bragginton, E.C.; Colenso, C.K.; Hirvonen, V.H.A.; Takebayashi, Y.; Spencer, J. β -Lactamases and β -Lactamase Inhibitors in the 21st Century. *J. Mol. Biol.* **2019**, *431*, 3472–3500. [[CrossRef](#)] [[PubMed](#)]
83. Zakhour, J.; El Ayoubi, L.E.W.; Kanj, S.S. Metallo-beta-lactamases: Mechanisms, treatment challenges, and future prospects. *Expert Rev. Anti-Infect. Ther.* **2024**, *22*, 189–201. [[CrossRef](#)] [[PubMed](#)]
84. Tan, X.; Kim, H.S.; Baugh, K.; Huang, Y.; Kadiyala, N.; Wences, M.; Singh, N.; Wenzler, E.; Bulman, Z.P. Therapeutic Options for Metallo- β -Lactamase-Producing Enterobacterales. *Infect. Drug Resist.* **2021**, *14*, 125–142. [[CrossRef](#)]
85. Tamma, P.D.; Doi, Y.; Bonomo, R.A.; Johnson, J.K.; Simner, P.J. A Primer on AmpC β -Lactamases: Necessary Knowledge for an Increasingly Multidrug-resistant World. *Clin. Infect. Dis.* **2019**, *69*, 1446–1455. [[CrossRef](#)]
86. Rodríguez-Baño, J.; Gutiérrez-Gutiérrez, B.; Machuca, I.; Pascual, A. Treatment of Infections Caused by Extended-Spectrum-Beta-Lactamase-, AmpC-, and Carbapenemase-Producing Enterobacteriaceae. *Clin. Microbiol. Rev.* **2018**, *31*. [[CrossRef](#)] [[PubMed](#)]
87. Mathers, A.J.; Hazen, K.C.; Carroll, J.; Yeh, A.J.; Cox, H.L.; Bonomo, R.A.; Sifri, C.D. First clinical cases of OXA-48-producing carbapenem-resistant *Klebsiella pneumoniae* in the United States: The “menace” arrives in the new world. *J. Clin. Microbiol.* **2013**, *51*, 680–683. [[CrossRef](#)] [[PubMed](#)]
88. Isler, B.; Aslan, A.T.; Akova, M.; Harris, P.; Paterson, D.L. Treatment strategies for OXA-48-like and NDM producing *Klebsiella pneumoniae* infections. *Expert Rev. Anti-Infect. Ther.* **2022**, *20*, 1389–1400. [[CrossRef](#)] [[PubMed](#)]
89. Pungartnik, P.C.; Abreu, A.; dos Santos, C.V.B.; Cavalcante, J.R.; Faerstein, E.; Werneck, G.L. The interfaces between One Health and Global Health: A scoping review. *One Health* **2023**, *16*, 100573. [[CrossRef](#)] [[PubMed](#)]
90. Mackenzie, J.S.; Jeggo, M. The One Health Approach-Why Is It So Important? *Trop. Med. Infect. Dis.* **2019**, *4*, 88. [[CrossRef](#)] [[PubMed](#)]
91. Muteeb, G.; Rehman, M.T.; Shahwan, M.; Aatif, M. Origin of Antibiotics and Antibiotic Resistance, and Their Impacts on Drug Development: A Narrative Review. *Pharmaceuticals* **2023**, *16*, 1615. [[CrossRef](#)] [[PubMed](#)]
92. McEwen, S.A.; Collignon, P.J. Antimicrobial Resistance: A One Health Perspective. *Microbiol. Spectr.* **2018**, *6*. [[CrossRef](#)]
93. Mendelson, M.; Laxminarayan, R.; Limmathurotsakul, D.; Kariuki, S.; Gyansa-Lutterodt, M.; Charani, E.; Singh, S.; Walia, K.; Gales, A.C.; Mpundu, M. Antimicrobial resistance and the great divide: Inequity in priorities and agendas between the Global North and the Global South threatens global mitigation of antimicrobial resistance. *Lancet Glob. Health* **2024**, *12*, e516–e521. [[CrossRef](#)] [[PubMed](#)]
94. Velazquez-Meza, M.E.; Galarde-López, M.; Carrillo-Quiróz, B.; Alpuche-Aranda, C.M. Antimicrobial resistance: One Health approach. *Vet. World* **2022**, *15*, 743–749. [[CrossRef](#)]
95. Aslam, B.; Khurshid, M.; Arshad, M.I.; Muzammil, S.; Rasool, M.; Yasmeen, N.; Shah, T.; Chaudhry, T.H.; Rasool, M.H.; Shahid, A.; et al. Antibiotic Resistance: One Health One World Outlook. *Front. Cell. Infect. Microbiol.* **2021**, *11*, 771510. [[CrossRef](#)]
96. Ma, L.; Li, B.; Jiang, X.-T.; Wang, Y.-L.; Xia, Y.; Li, A.-D.; Zhang, T. Catalogue of antibiotic resistome and host-tracking in drinking water deciphered by a large scale survey. *Microbiome* **2017**, *5*, 154. [[CrossRef](#)] [[PubMed](#)]
97. Leonard, A.F.C.; Zhang, L.; Balfour, A.J.; Garside, R.; Hawkey, P.M.; Murray, A.K.; Ukoumunne, O.C.; Gaze, W.H. Exposure to and colonisation by antibiotic-resistant *E. coli* in UK coastal water users: Environmental surveillance, exposure assessment, and epidemiological study (Beach Bum Survey). *Environ. Int.* **2018**, *114*, 326–333. [[CrossRef](#)] [[PubMed](#)]
98. Bengtsson-Palme, J.; Kristiansson, E.; Larsson, D.G.J. Environmental factors influencing the development and spread of antibiotic resistance. *FEMS Microbiol. Rev.* **2017**, *42*, 68–80. [[CrossRef](#)] [[PubMed](#)]
99. Al-Tawfiq, J.A.; Ebrahim, S.H.; Memish, Z.A. Preventing Antimicrobial Resistance Together: Reflections on AMR Week 2023. *J. Epidemiol. Glob. Health* **2024**, *14*, 249–251. [[CrossRef](#)] [[PubMed](#)]
100. Watts, J.E.M.; Schreier, H.J.; Lanska, L.; Hale, M.S. The Rising Tide of Antimicrobial Resistance in Aquaculture: Sources, Sinks and Solutions. *Mar. Drugs* **2017**, *15*, 158. [[CrossRef](#)] [[PubMed](#)]
101. Duarte, A.C.; Rodrigues, S.; Afonso, A.; Nogueira, A.; Coutinho, P. Antibiotic Resistance in the Drinking Water: Old and New Strategies to Remove Antibiotics, Resistant Bacteria, and Resistance Genes. *Pharmaceuticals* **2022**, *15*, 393. [[CrossRef](#)] [[PubMed](#)]
102. Amin, V.P.; Dhanani, M.; Patel, J.; Dhawan, A.; Mahesh, G.; Chenna, V.S.H.; Kyada, S.; Dekhne, A.; Desai, H.D. 2233. Burden of Bacterial Antimicrobial Resistance in United States in 2019: A Systematic Analysis. *Open Forum Infect. Dis.* **2023**, *10*, ofad500-1855. [[CrossRef](#)]
103. World Health Organization (WHO). *The Burden of Antimicrobial Resistance (AMR) in Mali*; Institute for Health Metrics and Evaluation: Seattle, WA, USA, 2023.
104. Institute for Health Metrics and Evaluation. *Bacterial Antimicrobial Resistance Burden Estimates 2019*; Institute for Health Metrics and Evaluation: Seattle, WA, USA, 2022.
105. Pokharel, S.; Raut, S.; Adhikari, B. Tackling antimicrobial resistance in low-income and middle-income countries. *BMJ Glob. Health* **2019**, *4*, e002104. [[CrossRef](#)]

106. Adebisi, Y.A.; Ogunkola, I.O. The global antimicrobial resistance response effort must not exclude marginalised populations. *Trop. Med. Health* **2023**, *51*, 33. [[CrossRef](#)]
107. Combes, A.; Luyt, C.E.; Fagon, J.Y.; Wolff, M.; Trouillet, J.L.; Chastre, J. Impact of piperacillin resistance on the outcome of *Pseudomonas* ventilator-associated pneumonia. *Intensive Care Med.* **2006**, *32*, 1970–1978. [[CrossRef](#)]
108. Amer, W. Effect of Carbapenem Resistant Metallo-Beta-Lactamase Positive *Pseudomonas aeruginosa* on Mortality and Morbidity of Intensive Care Unit Nosocomial Infections. *Int. J. Curr. Microbiol. Appl. Sci.* **2015**, *4*, 167–176.
109. Wells, G.; Shea, B.; O’Connell, D.; Peterson, j.; Welch, V.; Losos, M.; Tugwell, P. *The Newcastle–Ottawa Scale (NOS) for Assessing the Quality of Non-Randomized Studies in Meta-Analysis*; The Ottawa Hospital: Ottawa, ON, Canada, 2000.
110. Idris, F.N.; Nadzir, M.M. Multi-drug resistant ESKAPE pathogens and the uses of plants as their antimicrobial agents. *Arch. Microbiol.* **2023**, *205*, 115. [[CrossRef](#)] [[PubMed](#)]
111. Oliveira, D.M.P.D.; Forde, B.M.; Kidd, T.J.; Harris, P.N.A.; Schembri, M.A.; Beatson, S.A.; Paterson, D.L.; Walker, M.J. Antimicrobial Resistance in ESKAPE Pathogens. *Clin. Microbiol. Rev.* **2020**, *33*. [[CrossRef](#)] [[PubMed](#)]
112. Ravi, K.; Singh, B. ESKAPE: Navigating the Global Battlefield for Antimicrobial Resistance and Defense in Hospitals. *Bacteria* **2024**, *3*, 76–98. [[CrossRef](#)]
113. Founou, R.C.; Founou, L.L.; Essack, S.Y. Clinical and economic impact of antibiotic resistance in developing countries: A systematic review and meta-analysis. *PLoS ONE* **2017**, *12*, e0189621. [[CrossRef](#)] [[PubMed](#)]
114. Palmer GH, B.G. *Combating Antimicrobial Resistance and Protecting the Miracle of Modern Medicine*; National Academies Press (US): Washington, DC, USA, 2021.
115. World Health Organization (WHO). *WHO Bacterial Priority Pathogens List, 2024: Bacterial Pathogens of Public Health Importance to Guide Research, Development and Strategies to Prevent and Control Antimicrobial Resistance*; World Health Organization (WHO): Geneva, Switzerland, 2024.
116. Toner, E.; Adalja, A.; Gronvall, G.K.; Cicero, A.; Inglesby, T.V. Antimicrobial resistance is a global health emergency. *Health Secur.* **2015**, *13*, 153–155. [[CrossRef](#)] [[PubMed](#)]
117. Salam, M.A.; Al-Amin, M.Y.; Salam, M.T.; Pawar, J.S.; Akhter, N.; Rabaan, A.A.; Alqumber, M.A.A. Antimicrobial Resistance: A Growing Serious Threat for Global Public Health. *Healthcare* **2023**, *11*, 1946. [[CrossRef](#)] [[PubMed](#)]
118. Prestinaci, F.; Pezzotti, P.; Pantosti, A. Antimicrobial resistance: A global multifaceted phenomenon. *Pathog. Glob. Health* **2015**, *109*, 309–318. [[CrossRef](#)]
119. Lessa, F.C.; Sievert, D.M. Antibiotic Resistance: A Global Problem and the Need to Do More. *Clin. Infect. Dis.* **2023**, *77*, S1–S3. [[CrossRef](#)]
120. Mestrovic, T.; Robles Aguilar, G.; Swetschinski, L.R.; Ikuta, K.S.; Gray, A.P.; Davis Weaver, N.; Han, C.; Wool, E.E.; Gershberg Hayoon, A.; Hay, S.I.; et al. The burden of bacterial antimicrobial resistance in the WHO European region in 2019: A cross-country systematic analysis. *Lancet Public Health* **2022**, *7*, e897–e913. [[CrossRef](#)]
121. Planta, M.B. The role of poverty in antimicrobial resistance. *J. Am. Board Fam. Med.* **2007**, *20*, 533–539. [[CrossRef](#)] [[PubMed](#)]
122. Obua, C.; Talib, Z.; Haberer, J.E. Poverty and antibiotic misuse: A complex association. *Lancet Glob. Health* **2023**, *11*, e6–e7. [[CrossRef](#)] [[PubMed](#)]
123. Patel, J.; Harant, A.; Fernandes, G.; Mwamelo, A.J.; Hein, W.; Dekker, D.; Sridhar, D. Measuring the global response to antimicrobial resistance, 2020–2021: A systematic governance analysis of 114 countries. *Lancet Infect. Dis.* **2023**, *23*, 706–718. [[CrossRef](#)]
124. Jinks, T.; Lee, N.; Sharland, M.; Rex, J.; Gertler, N.; Diver, M.; Jones, I.; Jones, K.; Mathewson, S.; Chiara, F.; et al. A time for action: Antimicrobial resistance needs global response. *Bull. World Health Organ.* **2016**, *94*, 558–558A. [[CrossRef](#)] [[PubMed](#)]
125. Dutescu, I.A.; Hillier, S.A. Encouraging the Development of New Antibiotics: Are Financial Incentives the Right Way Forward? A Systematic Review and Case Study. *Infect. Drug Resist.* **2021**, *14*, 415–434. [[CrossRef](#)] [[PubMed](#)]
126. Cars, O.; Chandy, S.J.; Mpundu, M.; Peralta, A.Q.; Zorzet, A.; So, A.D. Resetting the agenda for antibiotic resistance through a health systems perspective. *Lancet Glob. Health* **2021**, *9*, e1022–e1027. [[CrossRef](#)] [[PubMed](#)]
127. Bloom, G.; Merrett, G.B.; Wilkinson, A.; Lin, V.; Paulin, S. Antimicrobial resistance and universal health coverage. *BMJ Glob. Health* **2017**, *2*, e000518. [[CrossRef](#)] [[PubMed](#)]
128. Anderson, M.; Panteli, D.; van Kessel, R.; Ljungqvist, G.; Colombo, F.; Mossialos, E. Challenges and opportunities for incentivising antibiotic research and development in Europe. *Lancet Reg. Health Eur.* **2023**, *33*, 100705. [[CrossRef](#)]
129. Morel, C.M.; Lindahl, O.; Harbarth, S.; de Kraker, M.E.A.; Edwards, S.; Hollis, A. Industry incentives and antibiotic resistance: An introduction to the antibiotic susceptibility bonus. *J. Antibiot.* **2020**, *73*, 421–428. [[CrossRef](#)]
130. Hyun, D. *Antibiotic Development Needs Economic Incentives*; The Pew Charitable Trusts: Philadelphia, PA, USA, 2021.
131. Brogan, D.M.; Mossialos, E. Incentives for new antibiotics: The Options Market for Antibiotics (OMA) model. *Globalization and Health* **2013**, *9*, 58. [[CrossRef](#)]
132. Hayes, J.F. Fighting Back against Antimicrobial Resistance with Comprehensive Policy and Education: A Narrative Review. *Antibiotics* **2022**, *11*, 644. [[CrossRef](#)] [[PubMed](#)]
133. Bankar, N.J.; Ugemuge, S.; Ambad, R.S.; Hawale, D.V.; Timilsina, D.R. Implementation of Antimicrobial Stewardship in the Healthcare Setting. *Cureus* **2022**, *14*, e26664. [[CrossRef](#)]
134. Calvo-Villamañán, A.; San Millán, Á.; Carrilero, L. Tackling AMR from a multidisciplinary perspective: A primer from education and psychology. *Int. Microbiol.* **2023**, *26*, 1–9. [[CrossRef](#)]

135. Mullins, L.P.; Mason, E.; Winter, K.; Sadarangani, M. Vaccination is an integral strategy to combat antimicrobial resistance. *PLoS Pathog.* **2023**, *19*, e1011379. [[CrossRef](#)]
136. Ren, M.; So, A.D.; Chandy, S.J.; Mpundu, M.; Peralta, A.Q.; Åkerfeldt, K.; Sjöblom, A.K.; Cars, O. Equitable Access to Antibiotics: A Core Element and Shared Global Responsibility for Pandemic Preparedness and Response. *J. Law Med. Ethics* **2022**, *50*, 34–39. [[CrossRef](#)] [[PubMed](#)]
137. Samreen; Ahmad, I.; Malak, H.A.; Abulreesh, H.H. Environmental antimicrobial resistance and its drivers: A potential threat to public health. *J. Glob. Antimicrob. Resist.* **2021**, *27*, 101–111. [[CrossRef](#)]
138. Larsson, D.G.J.; Flach, C.-F. Antibiotic resistance in the environment. *Nat. Rev. Microbiol.* **2022**, *20*, 257–269. [[CrossRef](#)]
139. Boyd, N.K.; Teng, C.; Frei, C.R. Brief Overview of Approaches and Challenges in New Antibiotic Development: A Focus On Drug Repurposing. *Front. Cell. Infect. Microbiol.* **2021**, *11*, 684515. [[CrossRef](#)] [[PubMed](#)]
140. Fisher, J.F.; Mobashery, S. Endless Resistance. Endless Antibiotics? *Medchemcomm* **2016**, *7*, 37–49. [[CrossRef](#)]
141. Klug, D.M.; Idiris, F.I.M.; Blaskovich, M.A.T.; von Delft, F.; Dowson, C.G.; Kirchhelle, C.; Roberts, A.P.; Singer, A.C.; Todd, M.H. There is no market for new antibiotics: This allows an open approach to research and development. *Wellcome Open Res.* **2021**, *6*, 146. [[CrossRef](#)]
142. Nathan, C.; Goldberg, F.M. The profit problem in antibiotic R&D. *Nat. Rev. Drug Discov.* **2005**, *4*, 887–891. [[CrossRef](#)] [[PubMed](#)]
143. Shafiq, N.; Pandey, A.K.; Malhotra, S.; Holmes, A.; Mendelson, M.; Malpani, R.; Balasegaram, M.; Charani, E. Shortage of essential antimicrobials: A major challenge to global health security. *BMJ Glob. Health* **2021**, *6*, e006961. [[CrossRef](#)] [[PubMed](#)]
144. Årdal, C.; Røttingen, J.-A.; Opalska, A.; Van Hengel, A.J.; Larsen, J. Pull Incentives for Antibacterial Drug Development: An Analysis by the Transatlantic Task Force on Antimicrobial Resistance. *Clin. Infect. Dis.* **2017**, *65*, 1378–1382. [[CrossRef](#)] [[PubMed](#)]
145. Cook, M.A.; Wright, G.D. The past, present, and future of antibiotics. *Sci. Transl. Med.* **2022**, *14*, eabo7793. [[CrossRef](#)] [[PubMed](#)]
146. Wasan, H.; Singh, D.; Reeta, K.H.; Gupta, Y.K. Landscape of Push Funding in Antibiotic Research: Current Status and Way Forward. *Biology* **2023**, *12*, 101. [[CrossRef](#)]
147. Schneider, M. New Rules Expand Application of the NTAP Program for Innovative Antibiotics. *Contagion* **2020**, *5*, 19–20.
148. Schurer, M.; Patel, R.; van Keep, M.; Horgan, J.; Matthijsse, S.; Madin-Warburton, M. Recent advances in addressing the market failure of new antimicrobials: Learnings from NICE’s subscription-style payment model. *Front. Med. Technol.* **2023**, *5*, 1010247. [[CrossRef](#)] [[PubMed](#)]
149. Towse, A.; Hoyle, C.K.; Goodall, J.; Hirsch, M.; Mestre-Ferrandiz, J.; Rex, J.H. Time for a change in how new antibiotics are reimbursed: Development of an insurance framework for funding new antibiotics based on a policy of risk mitigation. *Health Policy* **2017**, *121*, 1025–1030. [[CrossRef](#)]
150. Abdel Hadi, H.; Eltayeb, F.; Al Balushi, S.; Daghfal, J.; Ahmed, F.; Mateus, C. Evaluation of Hospital Antimicrobial Stewardship Programs: Implementation, Process, Impact, and Outcomes, Review of Systematic Reviews. *Antibiotics* **2024**, *13*, 253. [[CrossRef](#)]
151. Shively, N.R.; Morgan, D.J. The CDC antimicrobial use measure is not ready for public reporting or value-based programs. *Antimicrob. Steward Healthc. Epidemiol.* **2023**, *3*, e77. [[CrossRef](#)]
152. Kern, W.V. Organization of antibiotic stewardship in Europe: The way to go. *Wien. Med. Wochenschr.* **2021**, *171*, 4–8. [[CrossRef](#)] [[PubMed](#)]
153. Simjee, S.; Ippolito, G. European regulations on prevention use of antimicrobials from January 2022. *Braz. J. Vet. Med.* **2022**, *44*, e000822. [[CrossRef](#)] [[PubMed](#)]
154. Pierce, J.; Apisarnthanarak, A.; Schellack, N.; Cornistein, W.; Maani, A.A.; Adnan, S.; Stevens, M.P. Global Antimicrobial Stewardship with a Focus on Low- and Middle-Income Countries. *Int. J. Infect. Dis.* **2020**, *96*, 621–629. [[CrossRef](#)] [[PubMed](#)]
155. Gigante, V.; Sati, H.; Beyer, P. Recent advances and challenges in antibacterial drug development. *Admet Dmpk* **2022**, *10*, 147–151. [[CrossRef](#)] [[PubMed](#)]
156. Clancy, C.J.; Nguyen, M.H. Buying Time: The AMR Action Fund and the State of Antibiotic Development in the United States 2020. *Open Forum Infect. Dis.* **2020**, *7*, ofaa464. [[CrossRef](#)] [[PubMed](#)]
157. Mullard, A. Pharmaceutical firms commit US\$1 billion to antibiotic development. *Nat. Rev. Drug Discov.* **2020**, *19*, 575–576. [[CrossRef](#)] [[PubMed](#)]
158. Otterson, K. A Perspective on Incentives for Novel Inpatient Antibiotics: No One-Size-Fits-All. *J. Law Med. Ethics* **2018**, *46*, 59–65.
159. Quinn, G.A.; Dyson, P.J. Going to extremes: Progress in exploring new environments for novel antibiotics. *NPJ Antimicrob. Resist.* **2024**, *2*, 8. [[CrossRef](#)]
160. Hamrick, J.C.; Docquier, J.D.; Uehara, T.; Myers, C.L.; Six, D.A.; Chatwin, C.L.; John, K.J.; Vernacchio, S.F.; Cusick, S.M.; Trout, R.E.L.; et al. VNRX-5133 (Taniborbactam), a Broad-Spectrum Inhibitor of Serine- and Metallo- β -Lactamases, Restores Activity of Cefepime in Enterobacterales and *Pseudomonas aeruginosa*. *Antimicrob. Agents Chemother.* **2020**, *64*, e01963-19. [[CrossRef](#)]
161. Karlowsky, J.A.; Hackel, M.A.; Wise, M.G.; Six, D.A.; Uehara, T.; Daigle, D.M.; Cusick, S.M.; Pevear, D.C.; Moeck, G.; Sahn, D.F. In Vitro Activity of Cefepime-Taniborbactam and Comparators against Clinical Isolates of Gram-Negative Bacilli from 2018 to 2020: Results from the Global Evaluation of Antimicrobial Resistance via Surveillance (GEARS) Program. *Antimicrob. Agents Chemother.* **2023**, *67*, e01281-22. [[CrossRef](#)]
162. Gerges, B.; Rosenblatt, J.; Truong, Y.-L.; Jiang, Y.; Shelburne, S.A.; Chaftari, A.-M.; Hachem, R.; Raad, I. In vitro activity of cefepime/taniborbactam and comparator agents against Gram-negative bacterial bloodstream pathogens recovered from patients with cancer. *JAC-Antimicrob. Resist.* **2024**, *6*, dlac060. [[CrossRef](#)] [[PubMed](#)]

163. Meletiadis, J.; Paranos, P.; Georgiou, P.-C.; Vourli, S.; Antonopoulou, S.; Michelaki, A.; Vagiakou, E.; Pournaras, S. In vitro comparative activity of the new beta-lactamase inhibitor taniborbactam with cefepime or meropenem against *Klebsiella pneumoniae* and cefepime against *Pseudomonas aeruginosa* metallo-beta-lactamase-producing clinical isolates. *Int. J. Antimicrob. Agents* **2021**, *58*, 106440. [[CrossRef](#)] [[PubMed](#)]
164. Abdelraouf, K.; Nicolau, D.P. In vivo pharmacokinetic/pharmacodynamic evaluation of cefepime/taniborbactam combination against cefepime-non-susceptible Enterobacterales and *Pseudomonas aeruginosa* in a murine pneumonia model. *J. Antimicrob. Chemother.* **2023**, *78*, 692–702. [[CrossRef](#)] [[PubMed](#)]
165. Wagenlehner, F.M.; Gasink, L.B.; McGovern, P.C.; Moeck, G.; McLeroth, P.; Dorr, M.; Dane, A.; Henkel, T. Cefepime-Taniborbactam in Complicated Urinary Tract Infection. *N. Engl. J. Med.* **2024**, *390*, 611–622. [[CrossRef](#)] [[PubMed](#)]
166. Dowell, J.A.; Marbury, T.C.; Smith, W.B.; Henkel, T. Safety and Pharmacokinetics of Taniborbactam (VNRX-5133) with Cefepime in Subjects with Various Degrees of Renal Impairment. *Antimicrob. Agents Chemother.* **2022**, *66*, e00253-22. [[CrossRef](#)] [[PubMed](#)]
167. Dowell James, A.; Dickerson, D.; Henkel, T. Safety and Pharmacokinetics in Human Volunteers of Taniborbactam (VNRX-5133), a Novel Intravenous β -Lactamase Inhibitor. *Antimicrob. Agents Chemother.* **2021**, *65*. [[CrossRef](#)]
168. Abbott, C.; Satola, S.W.; Weiss, D.S. Heteroresistance to cefepime-taniborbactam in metallo- β -lactamase-encoding Enterobacterales. *Lancet Infect. Dis.* **2023**, *23*, e277–e278. [[CrossRef](#)] [[PubMed](#)]
169. Papp-Wallace, K.M.; Bethel, C.R.; Caillon, J.; Barnes, M.D.; Potel, G.; Bajaksouzian, S.; Rutter, J.D.; Reghal, A.; Shapiro, S.; Taracila, M.A.; et al. Beyond Piperacillin-Tazobactam: Cefepime and AAI101 as a Potent β -Lactam- β -Lactamase Inhibitor Combination. *Antimicrob. Agents Chemother.* **2019**, *63*, e00105-19. [[CrossRef](#)]
170. Vázquez-Ucha, J.C.; Lasarte-Monterrubio, C.; Guijarro-Sánchez, P.; Oviaño, M.; Álvarez-Fraga, L.; Alonso-García, I.; Arca-Suárez, J.; Bou, G.; Beceiro, A. Assessment of Activity and Resistance Mechanisms to Cefepime in Combination with the Novel β -Lactamase Inhibitors Zidebactam, Taniborbactam, and Enmetazobactam against a Multicenter Collection of Carbapenemase-Producing Enterobacterales. *Antimicrob. Agents Chemother.* **2022**, *66*, e01676-21. [[CrossRef](#)]
171. Kaye, K.S.; Belle, A.; Barth, P.; Lahlou, O.; Knechtle, P.; Motta, P.; Velicitat, P. Effect of Cefepime/Enmetazobactam vs Piperacillin/Tazobactam on Clinical Cure and Microbiological Eradication in Patients with Complicated Urinary Tract Infection or Acute Pyelonephritis: A Randomized Clinical Trial. *JAMA* **2022**, *328*, 1304–1314. [[CrossRef](#)]
172. Morrissey, I.; Magnet, S.; Hawser, S.; Shapiro, S.; Knechtle, P. In Vitro Activity of Cefepime-Enmetazobactam against Gram-Negative Isolates Collected from U.S. and European Hospitals during 2014–2015. *Antimicrob. Agents Chemother.* **2019**, *63*, e00514-19. [[CrossRef](#)] [[PubMed](#)]
173. Sader, H.S.; Mendes, R.E.; Duncan, L.R.; Carvalhaes, C.G.; Castanheria, M. Antimicrobial activity of cefepime/zidebactam (WCK 5222), a β -lactam/ β -lactam enhancer combination, against clinical isolates of Gram-negative bacteria collected worldwide (2018–19). *J. Antimicrob. Chemother.* **2022**, *77*, 2642–2649. [[CrossRef](#)] [[PubMed](#)]
174. Papp-Wallace, K.M.; Nguyen, N.Q.; Jacobs, M.R.; Bethel, C.R.; Barnes, M.D.; Kumar, V.; Bajaksouzian, S.; Rudin, S.D.; Rather, P.N.; Bhavsar, S.; et al. Strategic Approaches to Overcome Resistance against Gram-Negative Pathogens Using β -Lactamase Inhibitors and β -Lactam Enhancers: Activity of Three Novel Diazabicyclooctanes WCK 5153, Zidebactam (WCK 5107), and WCK 4234. *J. Med. Chem.* **2018**, *61*, 4067–4086. [[CrossRef](#)] [[PubMed](#)]
175. Yahav, D.; Giske, C.G.; Grämatniece, A.; Abodakpi, H.; Tam, V.H.; Leibovici, L. New β -Lactam- β -Lactamase Inhibitor Combinations. *Clin. Microbiol. Rev.* **2020**, *34*. [[CrossRef](#)] [[PubMed](#)]
176. Mushtaq, S.; Garello, P.; Vickers, A.; Woodford, N.; Livermore, D.M. Activity of cefepime/zidebactam (WCK 5222) against p'roblem' antibiotic-resistant Gram-negative bacteria sent to a national reference laboratory. *J. Antimicrob. Chemother.* **2021**, *76*, 1511–1522. [[CrossRef](#)] [[PubMed](#)]
177. Le Terrier, C.; Nordmann, P.; Sadek, M.; Poirel, L. In vitro activity of cefepime/zidebactam and cefepime/taniborbactam against aztreonam/avibactam-resistant NDM-like-producing *Escherichia coli* clinical isolates. *J. Antimicrob. Chemother.* **2023**, *78*, 1191–1194. [[CrossRef](#)] [[PubMed](#)]
178. Moya, B.; Barcelo, I.M.; Bhagwat, S.; Patel, M.; Bou, G.; Papp-Wallace, K.M.; Bonomo, R.A.; Oliver, A. Potent β -Lactam Enhancer Activity of Zidebactam and WCK 5153 against *Acinetobacter baumannii*, Including Carbapenemase-Producing Clinical Isolates. *Antimicrob. Agents Chemother.* **2017**, *61*. [[CrossRef](#)] [[PubMed](#)]
179. Moya, B.; Barcelo, I.M.; Bhagwat, S.; Patel, M.; Bou, G.; Papp-Wallace, K.M.; Bonomo, R.A.; Oliver, A. WCK 5107 (Zidebactam) and WCK 5153 Are Novel Inhibitors of PBP2 Showing Potent " β -Lactam Enhancer" Activity against *Pseudomonas aeruginosa*, Including Multidrug-Resistant Metallo- β -Lactamase-Producing High-Risk Clones. *Antimicrob. Agents Chemother.* **2017**, *61*. [[CrossRef](#)]
180. Karlowsky, J.A.; Hackel, M.A.; Bouchillon, S.K.; Sahm, D.F. In Vitro Activity of WCK 5222 (Cefepime-Zidebactam) against Worldwide Collected Gram-Negative Bacilli Not Susceptible to Carbapenems. *Antimicrob. Agents Chemother.* **2020**, *64*. [[CrossRef](#)]
181. Dubey, D.; Roy, M.; Shah, T.H.; Bano, N.; Kulshrestha, V.; Mitra, S.; Sangwan, P.; Dubey, M.; Imran, A.; Jain, B.; et al. Compassionate use of a novel β -lactam enhancer-based investigational antibiotic cefepime/zidebactam (WCK 5222) for the treatment of extensively-drug-resistant NDM-expressing *Pseudomonas aeruginosa* infection in an intra-abdominal infection-induced sepsis patient: A case report. *Ann. Clin. Microbiol. Antimicrob.* **2023**, *22*, 55. [[CrossRef](#)]

182. Tirlangi, P.K.; Wanve, B.S.; Dubbudu, R.R.; Yadav, B.S.; Kumar, L.S.; Gupta, A.; Sree, R.A.; Challa, H.P.R.; Reddy, P.N. Successful Use of Cefepime-Zidebactam (WCK 5222) as a Salvage Therapy for the Treatment of Disseminated Extensively Drug-Resistant New Delhi Metallo- β -Lactamase-Producing *Pseudomonas aeruginosa* Infection in an Adult Patient with Acute T-Cell Leukemia. *Antimicrob. Agents Chemother.* **2023**, *67*, e00500-23. [[CrossRef](#)]
183. Gootz, T.; Retsema, J.; Girard, A.; Hamanaka, E.; Anderson, M.; Sokolowski, S. In vitro activity of CP-65,207, a new penem antimicrobial agent, in comparison with those of other agents. *Antimicrob. Agents Chemother.* **1989**, *33*, 1160–1166. [[CrossRef](#)] [[PubMed](#)]
184. Komoto, A.; Otsuki, M.; Nishino, T. In vitro and in vivo antibacterial activities of sulopenem, a new penem antibiotic. *Jpn. J. Antibiot.* **1996**, *49*, 352–366. [[PubMed](#)]
185. Karlowsky, J.A.; Adam, H.J.; Baxter, M.R.; Denisuik, A.J.; Lagacé-Wiens, P.R.S.; Walkty, A.J.; Puttagunta, S.; Dunne, M.W.; Zhanel, G.G. In Vitro Activity of Sulopenem, an Oral Penem, against Urinary Isolates of *Escherichia coli*. *Antimicrob. Agents Chemother.* **2019**, *63*. [[CrossRef](#)]
186. Zhanel, G.G.; Pozdirca, M.; Golden, A.R.; Lawrence, C.K.; Zelenitsky, S.; Berry, L.; Schweizer, F.; Bay, D.; Adam, H.; Zhanel, M.A.; et al. Sulopenem: An Intravenous and Oral Penem for the Treatment of Urinary Tract Infections Due to Multidrug-Resistant Bacteria. *Drugs* **2022**, *82*, 533–557. [[CrossRef](#)] [[PubMed](#)]
187. Okamoto, K.; Gotoh, N.; Nishino, T. *Pseudomonas aeruginosa* reveals high intrinsic resistance to penem antibiotics: Penem resistance mechanisms and their interplay. *Antimicrob. Agents Chemother.* **2001**, *45*, 1964–1971. [[CrossRef](#)] [[PubMed](#)]
188. Chandra, R.; Hazra, A.; Skogerboe, T.; Labadie, R.; Kirby, D.; Soma, K.; Dunne, M. Pharmacokinetics (PK), safety, and tolerability of single doses of PF-03709270, with and without co-administration of probenecid Pfizer Global Research & Development. In *Abstracts Book, Interscience Conference On Antimicrobial Agents & Chemotherapy (Icaac)*; American Society For Microbiology: Washington, DC, USA, 2008.
189. Dunne, M.; Dunzo, E.; Puttagunta, S. A Phase 1 Study to Assess the Pharmacokinetics of Sulopenem Etzadroxil (PF-03709270). *Open Forum Infect. Dis.* **2017**, *4*, S525–S526. [[CrossRef](#)]
190. Dunne, M.W.; Das, A.F.; Zelasky, M.; Akinapelli, K.; Boucher, H.; Aronin, S.I. LB-1. Efficacy and Safety of Oral Sulopenem Etzadroxil/Probenecid Versus Oral Ciprofloxacin in the Treatment of Uncomplicated Urinary Tract Infections (uUTI) in Adult Women: Results from the SURE-1 Trial. *Open Forum Infect. Dis.* **2020**, *7*, S844. [[CrossRef](#)]
191. Dunne, M.W.; Aronin, S.I.; Das, A.F.; Akinapelli, K.; Zelasky, M.T.; Puttagunta, S.; Boucher, H.W. Sulopenem or Ciprofloxacin for the Treatment of Uncomplicated Urinary Tract Infections in Women: A Phase 3, Randomized Trial. *Clin. Infect. Dis.* **2023**, *76*, 66–77. [[CrossRef](#)]
192. Dunne, M.W.; Aronin, S.I. 1232. Efficacy and Safety of Intravenous Sulopenem Followed by Oral Sulopenem etzadroxil/Probenecid Versus Intravenous Ertapenem Followed by Oral Ciprofloxacin or Amoxicillin-clavulanate in the Treatment of Complicated Urinary Tract Infections (cUTI): Results from the SURE-2 Trial. *Open Forum Infect. Dis.* **2020**, *7*, S636.
193. Dunne, M.W.; Aronin, S.I.; Das, A.F.; Akinapelli, K.; Breen, J.; Zelasky, M.T.; Puttagunta, S. Sulopenem for the Treatment of Complicated Urinary Tract Infections Including Pyelonephritis: A Phase 3, Randomized Trial. *Clin. Infect. Dis.* **2023**, *76*, 78–88. [[CrossRef](#)] [[PubMed](#)]
194. Ehmann, D.E.; Jahic, H.; Ross, P.L.; Gu, R.F.; Hu, J.; Durand-Réville, T.F.; Lahiri, S.; Thresher, J.; Livchak, S.; Gao, N.; et al. Kinetics of avibactam inhibition against Class A, C, and D β -lactamases. *J. Biol. Chem.* **2013**, *288*, 27960–27971. [[CrossRef](#)] [[PubMed](#)]
195. Falcone, M.; Daikos, G.L.; Tiseo, G.; Bassoulis, D.; Giordano, C.; Galfò, V.; Leonildi, A.; Tagliaferri, E.; Barnini, S.; Sani, S.; et al. Efficacy of Ceftazidime-avibactam Plus Aztreonam in Patients with Bloodstream Infections Caused by Metallo- β -lactamase-Producing Enterobacterales. *Clin. Infect. Dis.* **2021**, *72*, 1871–1878. [[CrossRef](#)] [[PubMed](#)]
196. Sempere, A.; Viñado, B.; Los-Arcos, I.; Company, D.; Larrosa, N.; Fernández-Hidalgo, N.; Rodríguez-Pardo, D.; González-López, J.J.; Nuvials, X.; Almirante, B.; et al. Ceftazidime-Avibactam plus Aztreonam for the Treatment of Infections by VIM-Type-Producing Gram-Negative Bacteria. *Antimicrob. Agents Chemother.* **2022**, *66*, e00751-22. [[CrossRef](#)] [[PubMed](#)]
197. Mauri, C.; Maraolo, A.E.; Di Bella, S.; Luzzaro, F.; Principe, L. The Revival of Aztreonam in Combination with Avibactam against Metallo- β -Lactamase-Producing Gram-Negatives: A Systematic Review of In Vitro Studies and Clinical Cases. *Antibiotics* **2021**, *10*, 1012. [[CrossRef](#)] [[PubMed](#)]
198. Sader, H.S.; Carvalhaes, C.G.; Arends, S.J.R.; Castanheira, M.; Mendes, R.E. Aztreonam/avibactam activity against clinical isolates of Enterobacterales collected in Europe, Asia and Latin America in 2019. *J. Antimicrob. Chemother.* **2021**, *76*, 659–666. [[CrossRef](#)] [[PubMed](#)]
199. Principe, L.; Lupia, T.; Andriani, L.; Campanile, F.; Carcione, D.; Corcione, S.; De Rosa, F.G.; Luzzati, R.; Stroffolini, G.; Steyde, M.; et al. Microbiological, Clinical, and PK/PD Features of the New Anti-Gram-Negative Antibiotics: β -Lactam/ β -Lactamase Inhibitors in Combination and Cefiderocol—An All-Inclusive Guide for Clinicians. *Pharmaceuticals* **2022**, *15*, 463. [[CrossRef](#)] [[PubMed](#)]
200. Cornely, O.A.; Cisneros, J.M.; Torre-Cisneros, J.; Rodríguez-Hernández, M.J.; Tallón-Aguilar, L.; Calbo, E.; Horcajada, J.P.; Queckenberg, C.; Zettelmeyer, U.; Arenz, D.; et al. Pharmacokinetics and safety of aztreonam/avibactam for the treatment of complicated intra-abdominal infections in hospitalized adults: Results from the REJUVENATE study. *J. Antimicrob. Chemother.* **2020**, *75*, 618–627. [[CrossRef](#)] [[PubMed](#)]

201. Penwell, W.F.; Shapiro, A.B.; Giacobbe, R.A.; Gu, R.F.; Gao, N.; Thresher, J.; McLaughlin, R.E.; Huband, M.D.; DeJonge, B.L.; Ehmann, D.E.; et al. Molecular mechanisms of sulbactam antibacterial activity and resistance determinants in *Acinetobacter baumannii*. *Antimicrob. Agents Chemother.* **2015**, *59*, 1680–1689. [[CrossRef](#)]
202. Chu, H.; Zhao, L.; Wang, M.; Liu, Y.; Gui, T.; Zhang, J. Sulbactam-based therapy for *Acinetobacter baumannii* infection: A systematic review and meta-analysis. *Braz. J. Infect. Dis.* **2013**, *17*, 389–394. [[CrossRef](#)]
203. Ibrahim, S.; Al-Saryi, N.; Al-Kadmy, I.M.S.; Aziz, S.N. Multidrug-resistant *Acinetobacter baumannii* as an emerging concern in hospitals. *Mol. Biol. Rep.* **2021**, *48*, 6987–6998. [[CrossRef](#)] [[PubMed](#)]
204. Gonzalez-Villoria, A.M.; Valverde-Garduno, V. Antibiotic-Resistant *Acinetobacter baumannii* Increasing Success Remains a Challenge as a Nosocomial Pathogen. *J. Pathog.* **2016**, *2016*, 7318075. [[CrossRef](#)]
205. Jiang, Y.; Ding, Y.; Wei, Y.; Jian, C.; Liu, J.; Zeng, Z. Carbapenem-resistant *Acinetobacter baumannii*: A challenge in the intensive care unit. *Front. Microbiol.* **2022**, *13*, 1045206. [[CrossRef](#)] [[PubMed](#)]
206. Kaye, K.S.; Shorr, A.F.; Wunderink, R.G.; Du, B.; Poirier, G.E.; Rana, K.; Miller, A.; Lewis, D.; O'Donnell, J.; Chen, L.; et al. Efficacy and safety of sulbactam-durlobactam versus colistin for the treatment of patients with serious infections caused by *Acinetobacter baumannii*-calcoaceticus complex: A multicentre, randomised, active-controlled, phase 3, non-inferiority clinical trial (ATTACK). *Lancet Infect. Dis.* **2023**, *23*, 1072–1084. [[CrossRef](#)] [[PubMed](#)]
207. Watkins, R.R.; Bonomo, R.A. Sulbactam-durlobactam: A Step Forward in Treating Carbapenem-Resistant *Acinetobacter baumannii* (CRAB) Infections. *Clin. Infect. Dis.* **2023**, *76*, S163–S165. [[CrossRef](#)] [[PubMed](#)]
208. Papp-Wallace, K.M.; McLeod, S.M.; Miller, A.A. Durlobactam, a Broad-Spectrum Serine β -lactamase Inhibitor, Restores Sulbactam Activity Against *Acinetobacter* Species. *Clin. Infect. Dis.* **2023**, *76*, S194–S201. [[CrossRef](#)] [[PubMed](#)]
209. Durand-Réville, T.F.; Guler, S.; Comita-Prevoir, J.; Chen, B.; Bifulco, N.; Huynh, H.; Lahiri, S.; Shapiro, A.B.; McLeod, S.M.; Carter, N.M.; et al. ETX2514 is a broad-spectrum β -lactamase inhibitor for the treatment of drug-resistant Gram-negative bacteria including *Acinetobacter baumannii*. *Nat. Microbiol.* **2017**, *2*, 17104. [[CrossRef](#)] [[PubMed](#)]
210. McLeod, S.M.; Shapiro, A.B.; Moussa, S.H.; Johnstone, M.; McLaughlin, R.E.; de Jonge, B.L.M.; Miller, A.A. Frequency and Mechanism of Spontaneous Resistance to Sulbactam Combined with the Novel β -Lactamase Inhibitor ETX2514 in Clinical Isolates of *Acinetobacter baumannii*. *Antimicrob. Agents Chemother.* **2018**, *62*. [[CrossRef](#)] [[PubMed](#)]
211. McLeod, S.M.; Moussa, S.H.; Hackel, M.A.; Miller, A.A. In Vitro Activity of Sulbactam-Durlobactam against *Acinetobacter baumannii*-calcoaceticus Complex Isolates Collected Globally in 2016 and 2017. *Antimicrob. Agents Chemother.* **2020**, *64*. [[CrossRef](#)]
212. Principe, L.; Di Bella, S.; Conti, J.; Perilli, M.; Piccirilli, A.; Mussini, C.; Decorti, G. *Acinetobacter baumannii* Resistance to Sulbactam/Durlobactam: A Systematic Review. *Antibiotics* **2022**, *11*, 1793. [[CrossRef](#)]
213. Sun, D.; Tsivkovski, R.; Pogliano, J.; Tsunemoto, H.; Nelson, K.; Rubio-Aparicio, D.; Lomovskaya, O. Intrinsic Antibacterial Activity of Xeruborbactam In Vitro: Assessing Spectrum and Mode of Action. *Antimicrob. Agents Chemother.* **2022**, *66*, e00879-22. [[CrossRef](#)]
214. Lomovskaya, O.; Castanheira, M.; Lindley, J.; Rubio-Aparicio, D.; Nelson, K.; Tsivkovski, R.; Sun, D.; Totrov, M.; Loutit, J.; Dudley, M. In vitro potency of xeruborbactam in combination with multiple β -lactam antibiotics in comparison with other β -lactam/ β -lactamase inhibitor (BLI) combinations against carbapenem-resistant and extended-spectrum β -lactamase-producing Enterobacterales. *Antimicrob. Agents Chemother.* **2023**, *67*, e00440-23. [[CrossRef](#)] [[PubMed](#)]
215. Terrier, C.L.; Freire, S.; Viguier, C.; Findlay, J.; Nordmann, P.; Poirel, L. Relative inhibitory activities of the broad-spectrum β -lactamase inhibitor xeruborbactam in comparison with taniborbactam against metallo- β -lactamases produced in *Escherichia coli* and *Pseudomonas aeruginosa*. *Antimicrob. Agents Chemother.* **2024**, *68*, e01570-23. [[CrossRef](#)] [[PubMed](#)]
216. Lomovskaya, O.; Castanheira, M.; Lindley, J. 1693. Meropenem-Xeruborbactam: In Vitro Potency against Gram-Negative Bacteria in Comparison with Marketed and Investigational Beta-lactam (BL)/Beta-lactamase Inhibitor (BLI) Combinations. *Open Forum Infect. Dis.* **2022**, *9*, ofac492-1323. [[CrossRef](#)]
217. Griffith, D.; Roberts, J.; Wallis, S.; Hernandez-Mitre, M.P.; Morgan, E.; Dudley, M.; Loutit, J. 218. A Phase 1 Study of the Single-Dose Safety, Tolerability, and Pharmacokinetics of the Beta-lactamase inhibitor Xeruborbactam Administered as the Isobutyryloxymethyl Oral Prodrug to Healthy Adult Subjects. *Open Forum Infect. Dis.* **2022**, *9*, ofac492-296. [[CrossRef](#)]
218. Tarazi, Z.; Roos, N.; Page, T.; Griffith, D. 614. Pharmacodynamics (PD) of the Beta-Lactamase Inhibitor Xeruborbactam When Administered as the Oral Prodrug in Combination with Ceftibuten. *Open Forum Infect. Dis.* **2022**, *9*, ofac492-666. [[CrossRef](#)]
219. Mallalieu, N.L.; Winter, E.; Fettner, S.; Patel, K.; Zwanziger, E.; Attley, G.; Rodriguez, L.; Kano, A.; Salama, S.M.; Bentley, D.; et al. Safety and Pharmacokinetic Characterization of Nacubactam, a Novel β -Lactamase Inhibitor, Alone and in Combination with Meropenem, in Healthy Volunteers. *Antimicrob. Agents Chemother.* **2020**, *64*. [[CrossRef](#)]
220. Igarashi, Y.; Takemura, W.; Liu, X.; Kojima, N.; Morita, T.; Chuang, V.T.G.; Enoki, Y.; Taguchi, K.; Matsumoto, K. Development of an optimized and practical pharmacokinetics/pharmacodynamics analysis method for aztreonam/nacubactam against carbapenemase-producing *K. pneumoniae*. *J. Antimicrob. Chemother.* **2023**, *78*, 991–999. [[CrossRef](#)]
221. Kaushik, A.; Ammerman, N.C.; Parrish, N.M.; Nuermberger, E.L. New β -Lactamase Inhibitors Nacubactam and Zidebactam Improve the In Vitro Activity of β -Lactam Antibiotics against Mycobacterium abscessus Complex Clinical Isolates. *Antimicrob. Agents Chemother.* **2019**, *63*. [[CrossRef](#)]
222. Barnes, M.D.; Taracila, M.A.; Good, C.E.; Bajaksouzian, S.; Rojas, L.J.; van Duin, D.; Kreiswirth, B.N.; Jacobs, M.R.; Haldimann, A.; Papp-Wallace, K.M.; et al. Nacubactam Enhances Meropenem Activity against Carbapenem-Resistant *Klebsiella pneumoniae* Producing KPC. *Antimicrob. Agents Chemother.* **2019**, *63*. [[CrossRef](#)]

223. Gaynes, R. The Discovery of Penicillin—New Insights After More Than 75 Years of Clinical Use. *Emerg. Infect. Dis.* **2017**, *23*, 849–853. [[CrossRef](#)]
224. Fleming, A. The Discovery of Penicillin. *Br. Med. Bull.* **1944**, *2*, 4–5. [[CrossRef](#)]
225. Aminov, R.I. A brief history of the antibiotic era: Lessons learned and challenges for the future. *Front. Microbiol.* **2010**, *1*, 134. [[CrossRef](#)] [[PubMed](#)]
226. Ribeiro da Cunha, B.; Fonseca, L.P.; Calado, C.R.C. Antibiotic Discovery: Where Have We Come from, Where Do We Go? *Antibiotics* **2019**, *8*, 45. [[CrossRef](#)] [[PubMed](#)]
227. Caron, W.P.; Mousa, S.A. Prevention strategies for antimicrobial resistance: A systematic review of the literature. *Infect. Drug Resist.* **2010**, *3*, 25–33. [[CrossRef](#)] [[PubMed](#)]
228. Uchil, R.R.; Kohli, G.S.; Katekhaye, V.M.; Swami, O.C. Strategies to combat antimicrobial resistance. *J. Clin. Diagn. Res.* **2014**, *8*, Me01–Me04. [[CrossRef](#)]
229. Diaz, A.; Antonara, S.; Barton, T. Prevention Strategies to Combat Antimicrobial Resistance in Children in Resource-Limited Settings. *Curr. Trop. Med. Rep.* **2018**, *5*, 5–15. [[CrossRef](#)]
230. Rump, B.; Timen, A.; Hulscher, M.; Verweij, M. Infection control measures in times of antimicrobial resistance: A matter of solidarity. *Monash Bioeth. Rev.* **2020**, *38*, 47–55. [[CrossRef](#)] [[PubMed](#)]
231. Drwiega, E.N.; Griffith, N.; Herald, F.; Badowski, M.E. How to design and implement an outpatient antimicrobial stewardship programme. *Drugs Context* **2023**, *12*. [[CrossRef](#)]
232. Amin, A.N.; Dellinger, E.P.; Harnett, G.; Kraft, B.D.; LaPlante, K.L.; LoVecchio, F.; McKinnell, J.A.; Tillotson, G.; Valentine, S. It's about the patients: Practical antibiotic stewardship in outpatient settings in the United States. *Front. Med.* **2022**, *9*, 901980. [[CrossRef](#)]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.