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REVIEW ARTICLE FIDSA

# Drugs for Gram-Negative Bugs From 2010–2019: A Decade in Review

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A literature review spanning January 1, 2010, to December 31, 2019, was conducted using the PubMed and ISI Web of Science databases to determine the breadth of publication activity in the area of gram-negative bacteria antimicrobial therapy. The number of articles was used as a reflection of scholarly activity. First, PubMed was searched using the following Medical Subject Headings (MeSH): antibacterial agents, *Enterobacteriaceae*, *Acinetobacter*, and *Pseudomonas*. A total of 12 643 articles were identified within PubMed, and 77 862 articles were identified within ISI Web of Science that included these terms. Second, these articles were categorized by antibiotic class to identify relative contributions to the literature by drug category. Third, these studies were used to identify key trends in the treatment of gram-negative bacterial infections from the past decade. This review highlights advances made in the past 10 years in antibacterial pharmacotherapy and some of the challenges that await the next decade of practice.

**Keywords.** *Acinetobacter*; antibacterial pharmacotherapy; gram-negative bacteria; *Enterobacteriaceae*; *Pseudomonas*.

Gram-negative bacteria, specifically gram-negative rods (GNRs), are ubiquitous microorganisms that commonly feature a lipopolysaccharide-adorned outer membrane, a narrow peptidoglycan layer, and an inner membrane that effectively serve as permeability barriers to exogenous chemicals, including antibiotics [1]. GNRs acquire a variety of resistance traits via horizontal gene transfer, including drug efflux permeases, antibiotic-modifying enzymes, bypass targets, and ribosome modification or mutation [1, 2]. While genes encoding drug efflux permeases and antibiotic-modifying enzymes (eg, β-lactamases) are often acquired through horizontal gene transfer, mutational events are known to produce new phenotypes with modified antibiotic targets (eg, ribosomal mutation), resulting in diminished antibiotic–target interactions [3, 4]. In particular, β-lactamases play a critical role in catalyzing resistance against β-lactam antibiotics. Through repeated exposure, GNRs have developed extended-spectrum β-lactamases (ESBLs), which can confer resistance to penicillins and cephalosporins, and carbapenemases, which can confer resistance to carbapenems [5].

Gram-negative bacteria are responsible for a multitude of infections, including bacteremia, device-associated infections, intraabdominal infections (IAIs), urinary tract infections (UTIs), community-acquired bacterial pneumonia (CABP), hospital-acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP) [1]. Within these disease categories, GNRs compose a significant disease burden, causing upwards of 30% of hospital-acquired infections [6]. Multidrug-resistant (MDR) GNRs, including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and ESBL-producing *Enterobacteriaceae* worldwide are associated with poor patient prognosis [7]. (The family *Enterobacteriaceae* is a member of the reclassified phylogenetic order *Enterobacterales* [8].) The exponential growth of such MDR pathogens during the past decades demands a renewed interest in drug discovery and drug development in the search for antibiotics with novel mechanisms. For example, the emergence of multidrug-resistant GNRs educed the repurposing of polymyxins and fosfomycin as antibiotics of "last resort" in the mid-2000s [9, 10]. Furthermore, the disease burden of MDR pathogens has precipitated advances in practice development and scholarly activity during the last decade.

The Generating Antibiotics Incentives Now (GAIN) Act was signed into law on July 9, 2012, as part of the Food and Drug Administration Safety and Innovation Act (FDASIA) [7]. The purpose of the GAIN Act was to bolster drug development efforts for the treatment of microorganisms that were growing resistant to antimicrobials in the current formulary. The GAIN Act established the designation of certain new anti-infective agents as qualified infectious disease products (QIDPs) if they treated serious or life-threatening infections caused by emerging infectious disease pathogens or specific MDR pathogens identified by the FDA. In the past decade, 12 new antibiotics have been approved using the QIDP designation (Supplementary Appendix A). Eleven of the drugs that were approved using the

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QIDP designation were approved after the publication of the GAIN Act. These agents have been approved for a variety of infections including complicated urinary tract infections (cUTIs), CABP, HAP, VAP, acute bacterial skin and soft tissue infections (ABSSSIs), traveler's diarrhea, and complicated intra-abdominal infections (cIAIs). Under the GAIN Act, new antimicrobials have been approved in virtually every drug class used for the treatment of gram-negative bacterial infections. Three of these agents are of the cephalosporin class or are novel cephalosporin/β-lactamase inhibitors, including ceftolozane/tazobactam, ceftazidime/avibactam, and cefiderocol. The others include the carbapenem/β-lactamase inhibitors meropenem/vaborbactam and imipenem/cilastatin/relebactam, a new fluoroquinolone delafloxacin, tetracycline-family antibiotics eravacycline (a fluorocycline) and omadacycline (an aminomethylcycline), and a new aminoglycoside, plazomicin. Therefore, we conducted a literature review of publications and citations concerning the broad subject of antimicrobial pharmacotherapy of gram-negative bacteria. Using the identified publications, several topics were investigated: (1) trends in scholarship concerning treatment of infections caused by gram-negative bacteria; (2) popularity of drug classes by scholarly interest; (3) novel challenges, opportunities, and themes within prescribing practices; (4) how new drugs approved under the GAIN Act are used in clinical practice.

## RESULTS AND DISCUSSION

### Literature Review of Gram-Negative Antimicrobial Pharmacotherapy

First, search criteria were established for PubMed and ISI Web of Science to locate publications and citations about the use of gram-negative antimicrobials. Search criteria for PubMed were developed using Medical Subject Headings (MeSH) and included the following MeSH terms as major topics: "anti-microbial," "*Pseudomonas*," "*Acinetobacter*," and "*Enterobacteriaceae*" (Supplementary Appendix B). Simultaneously, a similar set of criteria was developed to search ISI Web of Science for articles with the same topical coverage (Figure 1). These initial search criteria resulted in the identification of 12 643 records in PubMed and 77 862 records in ISI Web of Science (Figure 2).

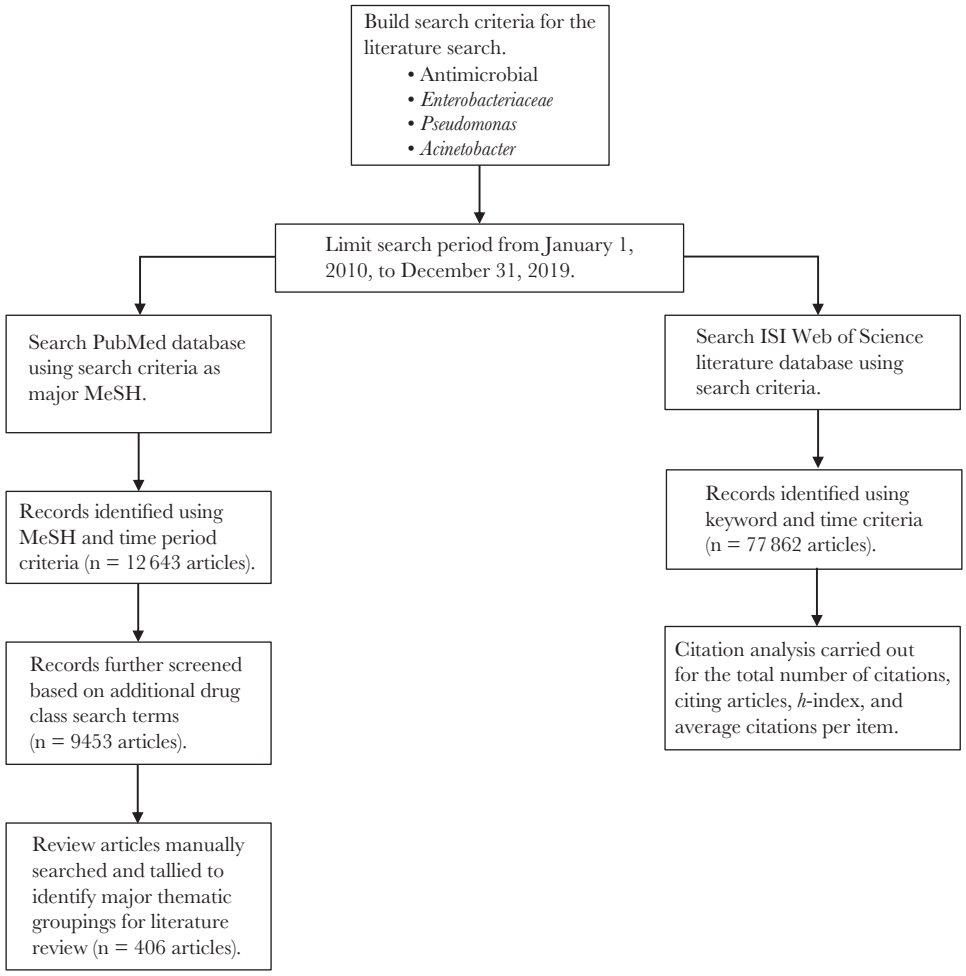


**Figure 1.** Literature search strategy and results. Abbreviation: MeSH, Medical Subject Headings.

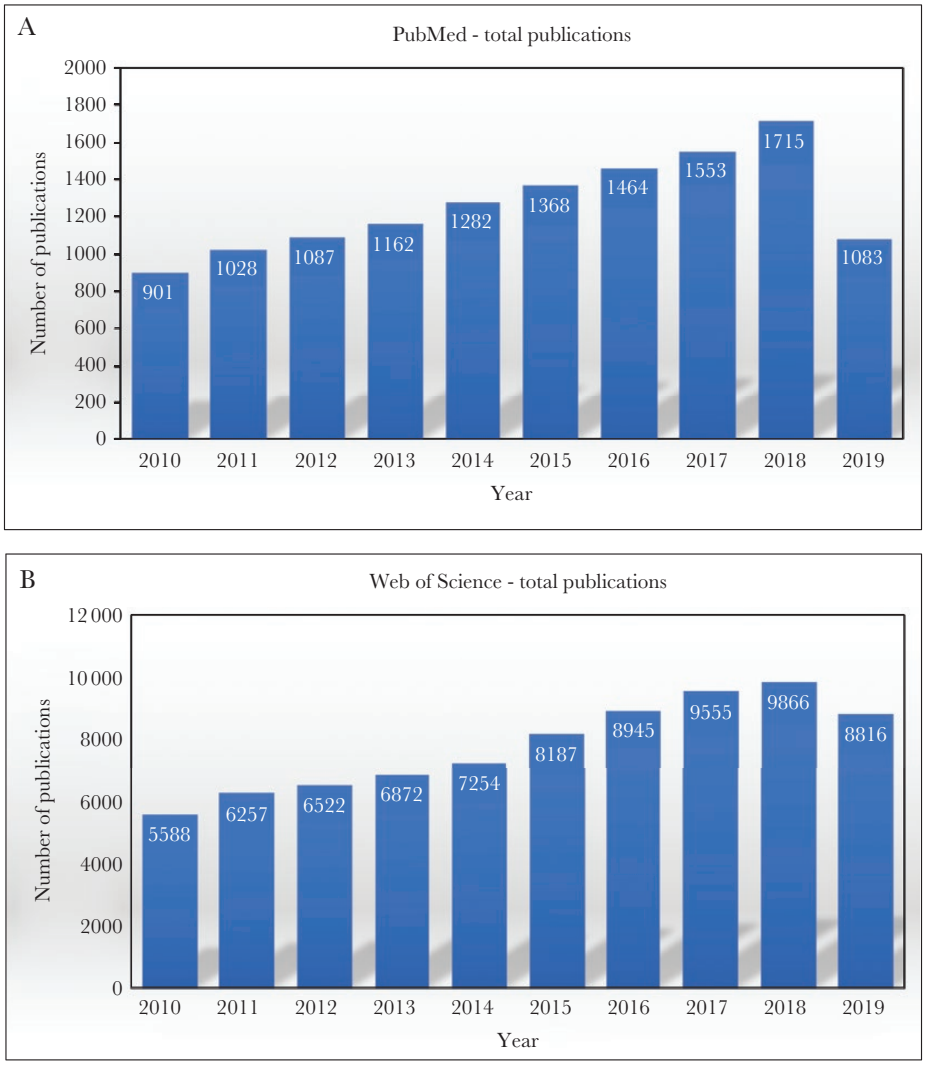


**Figure 2.** Total number of publications about gram-negative antimicrobials published from 2010 to 2019. A, The total number of publications indexed in PubMed. B, The total number of publications indexed in ISI Web of Science.

Importantly, it was noted that in both database searches, the total number of publications in this area increased linearly during the period of 2010–2018 (Figure 2). From the PubMed database, the number of publications increased per annum from 901 publications in 2010 to 1715 publications in 2018. In the ISI Web of Science search, the number of publications increased from 5588 in 2010 to 9866 publications in 2018. Notably, there was a decrease in the number of reported publications in 2019, which is hypothesized to be due to the delay in indexing of articles. We observed a nearly 2-fold increase in publication activity in the field of gram-negative antimicrobial pharmacotherapy during the 2010s.

Second, using the same search criteria, citation analysis was conducted using the results from ISI Web of Science. Citation analysis differs from the number of total publications in that it identifies the number of times publications were cited in other peer-reviewed articles for a given period. This reflects the impact, or the extent of dissemination, of a group of peer-reviewed articles. The citation analysis quantified the total number of citations that articles received in a given year (Figure 3). Articles that were published earlier in the decade accumulated more total citations than articles that were published later in the decade, as older articles have had more time to be discovered and cited. For example, articles published in 2010 were cited 183 032 times by 133 212 articles, as compared with fewer citations in 2019, in which 13 984 articles were cited by 11 540 articles. Also, articles published during this time exhibited an *h*-index of 139 in 2010 and 31 in 2019 (Figure 3). The *h*-index is a reflection of the number of publications "*h*," which have "*h*" number of citations; this is a useful metric for discriminating publications that are not yet cited and publications with a disproportionately high number of citations [11]. The average number of citations per item was 32.75 in 2010 and 3 in 2019. The data reveal broad dissemination and the high impact of

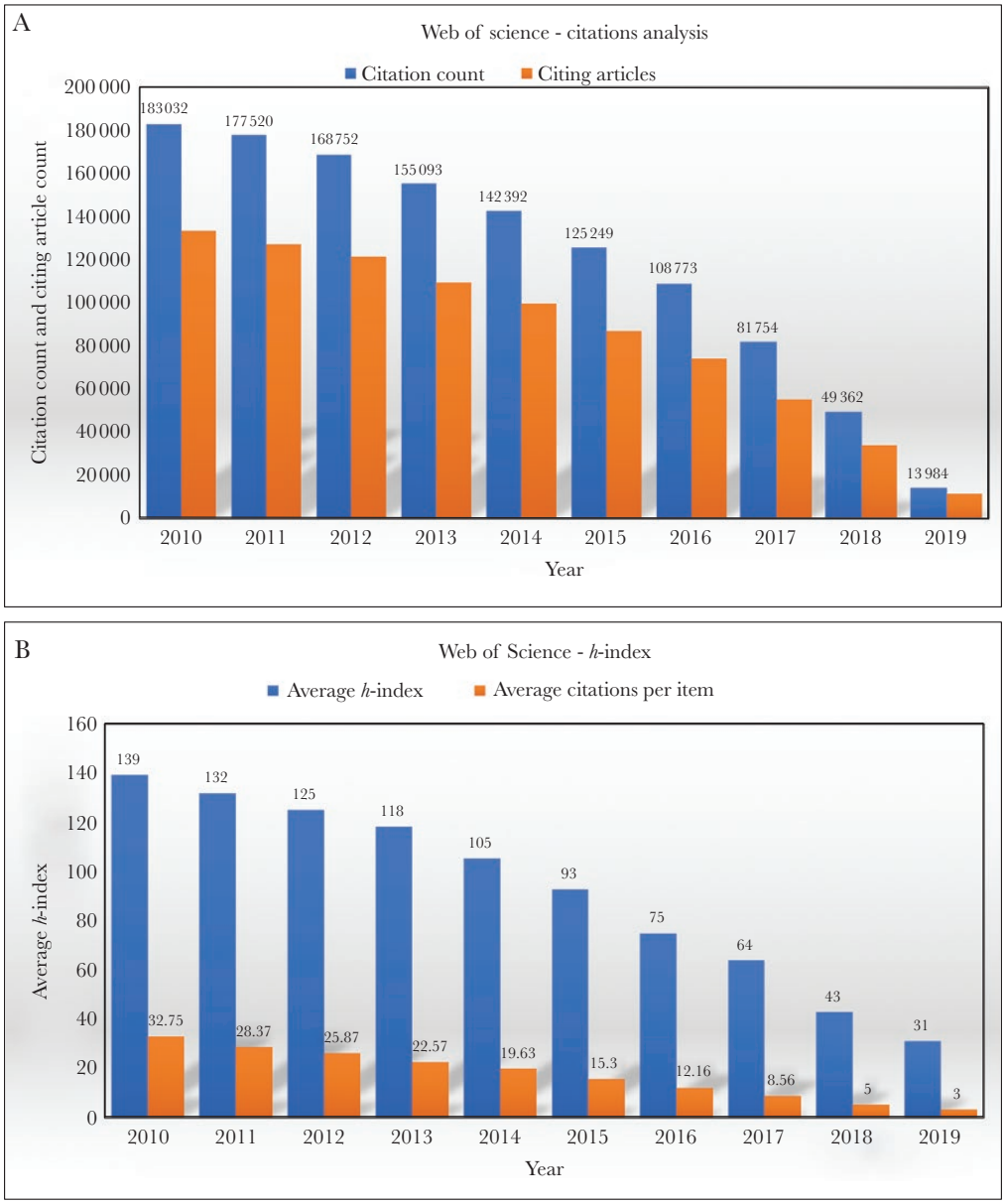


**Figure 3.** Citation analysis of publications from 2010–2019 from a Web of Science literature search. A, Total citation count and the number of citing articles and (B) Average *h*-index and average citations per item.

research in the field of gram-negative pharmacotherapy during the 2010s.

Third, an analysis of the total number of publications by drug class was also conducted (Figure 4). First, additional search terms for "penicillins," "cephalosporins," "aminoglycosides," "fluoroquinolones," "carbapenems," and "polymyxins" were included in the original search criteria in PubMed (Supplementary Appendix B). From these searches, the number of publications per drug class was quantified per annum over the course of the decade (Supplementary Appendix C). The data revealed a steady publication rate for aminoglycosides, fluoroquinolones, and penicillins over the course of the decade. There were notable increases in the number of publications for cephalosporins from 2016 to 2018, carbapenems from 2014 to 2017, and polymyxins from 2014 to 2017. The polymyxins exhibited the most dramatic increase in publications, from 138 articles in 2015 to 202 articles in 2016. This increase likely reflected the increase in use of these antimicrobial agents in practice. A pie chart was compiled reflecting the percentage of publications from each drug class that composed the body of work during the 2010s (Figure 4). Approximately 25% of the articles were not categorized using the drug class–specific search criteria. These data reflect an increase in scholarly activity for cephalosporins, carbapenems, and polymyxins in the pharmacotherapy

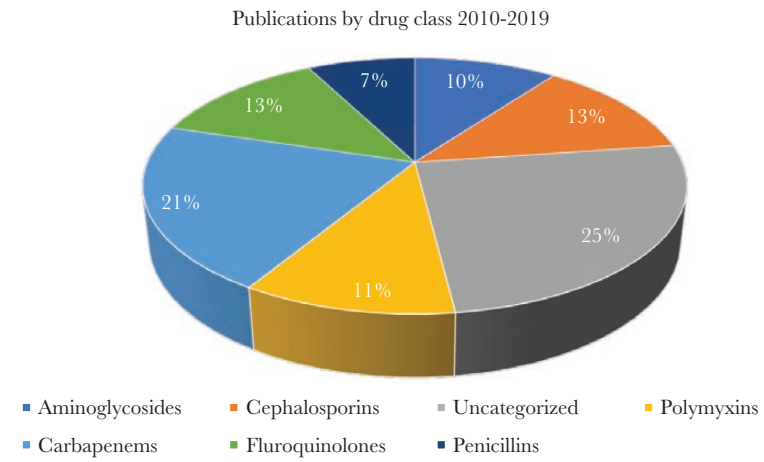


**Figure 4.** Percent contribution of total publications per drug class from 2010–2019.

of gram-negative bacterial infections during the last half of the decade and relatively constant scholarly activity for penicillins, aminoglycosides, and fluoroquinolones during the 2010s.

#### Thematic Analysis of Major Topics

Using the results of the literature review, the publications were narrowed down to review articles spanning January 1, 2010, to December 31, 2019, retrieved from PubMed to identify major publication themes. From this search, 407 review articles were identified and manually classified by publication themes via reading the title of the article and the abstract. From this, full-text publications of articles that encapsulated major publication "themes" were retrieved (Table 1).

The most common theme identified was the study of and management of infections caused by MDR bacteria. Throughout the 2010s, researchers focused on studying and reporting on inherently resistant GNRs such as *Pseudomonas aeruginosa* and *Acinetobacter baumanii* [12–16]. These organisms display resistance to antibiotics commonly used for community-acquired infections such as ceftriaxone and amoxicillin/clavulanic acid and can become resistant to other broad-spectrum antibiotics such as aminoglycosides, carbapenems, and polymyxins. During this time, many manuscripts were also published that described organisms that produce carbapenemases, such as *Klebsiella pneumoniae* carbapenemases (KPCs) and New Delhi metallo-β-lactamase (NDM) [17–23]. Treating *Enterobacteriaceae* that produce carbapenemases can offer a clinical challenge as they can also be resistant to non-β-lactam-class antibiotics due to the coexistence of other resistance mechanisms [24].

**Table 1. Evaluation of Literature Topics via Thematic Analysis**

| Topic | No. |
|---|---|
| Pharmacotherapy of MDR bacteria | 95 |
| Generalized MDR gram-negative pathogens (KPC, NDM, OXA-48, VIM, IMP) | 58 |
| *Pseudomonas* | 53 |
| *Acinetobacter* | 45 |
| Cystic fibrosis management | 32 |
| Resistance mechanisms | 24 |
| Specific antimicrobial agents | 22 |
| Specific diseases | 20 |
| Animal topics | 16 |

The table includes the evaluation of major themes of 407 review articles. As some review articles did not fit within any of these major themes, the numbers in the table will not add up to 407.

Abbreviations: KPC, *Klebsiella pneumoniae* carbapenemase-producing bacteria; MDR, multidrug-resistant; NDM, New Delhi metallo-β-lactamase 1-producing *Enterobacteriaceae*; OXA-48, oxacillinase/carbapenemase-producing *Klebsiella pneumoniae*; VIM, Verona integron-mediated metallo-β-lactamase-producing GNRs.

The second most common theme was the management of pulmonary infection in patients with cystic fibrosis. Throughout the 2010s, several review articles evaluating the optimal method of antibiotic delivery in these patients were published. Inhaled antibiotics had been used before the 2010s, but the optimal use of this method of antibiotic delivery was further evaluated [25–30]. Several oral and intravenous antibiotics were also investigated in inhaled formulations [31–35]. Additionally, the use of bronchoscopy-guided antimicrobial therapy was revisited throughout the decade [36–38]. Lastly, the management of *P. aeruginosa* specifically was the subject of many review articles, as it is one of the most common pathogens associated with acute and chronic cystic fibrosis infections [39–42].

The final theme identified during the review involved the use of antibiotics in animals and the subsequent development of resistance [43–46]. Antibiotics are commonly used as a growth promoter in livestock that are not infected. This practice leads to prolonged antibiotic exposure, which may promote the continued evolution of antimicrobial resistance. As of January 1, 2017, the FDA forbade the use of medically important antibiotics to promote growth in food animals [47]. This ruling likely contributed to an overall decrease in the sales of antimicrobials for use in animal feed from 2015,

which was the year of peak use, but sales did increase between 2017 and 2018 [47]. This theme is likely to receive further attention in the coming decade.

An exceedingly important theme of the decade that was not captured by this evaluation was the increased focus on antimicrobial stewardship. The Centers for Disease Control and Prevention (CDC) had a focus on antimicrobial stewardship before the 2010s with their "Get Smart" program, which was amplified in the following decade [48]. Throughout the 2010s, the CDC produced several evidence-based guidance documents, starting with the original CDC Core Elements of Hospital Antibiotic Stewardship Programs in 2014 [49–51]. These documents outlined evidence-based strategies for the creation and maintenance of impactful antimicrobial stewardship programs in the inpatient and outpatient setting. In tandem, the Joint Commission created new requirements for health care organizations to create and maintain inpatient and outpatient stewardship programs in accordance with the CDC Core Elements in 2017 and 2020, respectively [52, 53]. This renewed focus on antimicrobial stewardship by the federal government was accompanied by research into the topic. In particular, treating infections for decreasing durations was investigated, with the prevailing conclusion being that shorter durations of therapy are as effective as longer durations of therapy [54, 55].

#### Review of New Antibiotics Approved Under the GAIN Act

Treatment of resistant *Enterobacteriaceae* poses a clinical challenge, and in the early 2010s, there were few effective antibiotics. For MDR GNRs that are resistant to carbapenems, treatment options included toxic antibiotics such as polymyxins and aminoglycosides or antibiotics with increased risk for mortality such as tigecycline. Unfortunately, there exist some strains of bacteria that are also resistant to these antibiotics. Before 2014, when the first QIDPs were approved under the GAIN Act, many researchers investigated the efficacy of combination antibiotic therapy. The specific combinations recommended depended on the species of bacteria and that strain's specific susceptibility patterns. Possible regimens included combinations of polymyxins, carbapenems, aminoglycosides, tigecycline, fosfomycin, and the β-lactamase inhibitor sulbactam [56–59]. As antibiotics with activity against carbapenem-resistant *Enterobacteriaceae* (CRE) were approved throughout the decade, combination therapy became necessary in fewer cases. In the latter half of the decade, there was less research done into combination therapy and more investigation into repurposing older antibiotics to be used in combination therapy in the management of MDR bacteria, such as the use of minocycline in combination with carbapenems or polymyxins in the treatment of *A. baumanii* [60].

The reason for less interest in combination therapy in the latter half of the decade could be due to several new antibiotics with activity against MDR GNRs being approved between 2014 and 2019 through the GAIN Act. A large focus of research during this time was how to most effectively utilize these new antibiotics.

##### *Ceftolozane/Tazobactam*

Ceftolozane/tazobactam is a combination of the extended-spectrum cephalosporin ceftolozane and the β-lactamase inhibitor tazobactam. Ceftolozane is unique in its ability to overcome several defense mechanisms of *P. aeruginosa*. When compared with the third-generation cephalosporin ceftazidime, ceftolozane has stability in the presence of AmpC β-lactamases, which are common in *P. aeruginosa*, has 2-fold higher potency against penicillin-binding proteins, and is not a substrate for carbapenem-specific porins or efflux pumps found in *P. aeruginosa* [61–63]. Unfortunately, ceftolozane is susceptible to hydrolysis from some ESBLs, which is why it is packaged with tazobactam, to broaden ceftolozane's activity [64]. Overall, ceftolozane/tazobactam's main place in therapy is in the treatment of infections caused by MDR *P. aeruginosa* due to this cephalosporin combination's unique resiliency against many of MDR *P. aeruginosa*'*s* common resistance mechanisms.

##### *Ceftazidime/Avibactam*

Ceftazidime is a third-generation cephalosporin with broad-spectrum activity against gram-negative aerobes, including *P. aeruginosa*. Avibactam is a novel β-lactamase inhibitor with activity against a variety of β-lactamases including Ambler class A (TEM-1, CTX-M, SHV, KPC-2, and KPC-3), class C (AmpC), and certain class D (OXA-10 and OXA-48) [65–69]. Avibactam does not have activity against class B metallo β-lactamases (eg, NDM-1, VIM, and IMP) [67]. When compared with ceftolozane/tazobactam, ceftazidime/avibactam has greater activity against carbapenemase-producing CRE but has less activity against MDR *P. aeruginosa* isolates [70]. Overall, ceftazidime/avibactam's role in therapy is in the treatment of infections caused by CRE that produce specific β-lactamases, such as KPC and OXA-48, that are effectively inhibited by avibactam.

##### *Delafloxacin*

Like the other fluoroquinolones, delafloxacin works by targeting DNA gyrase and topoisomerase IV to halt bacterial replication. For gram-negative bacteria, fluoroquinolones primarily target DNA gyrase, while for gram-positive bacteria, fluoroquinolones primarily target topoisomerase IV [71]. Delafloxacin is unique among fluoroquinolones in that it is equally potent against both DNA gyrase and topoisomerase IV, which may contribute to increased potency against resistant organisms [72]. While delafloxacin is effective against fluoroquinolone-resistant MRSA, it has limited efficacy against *P. aeruginosa*, *A. baumanii*, carbapenemase-producing *E. coli*,

and carbapenemase-producing *K. pneumoniae* [73–75]. Overall, like other currently available systemic fluoroquinolones, delafloxacin is of limited clinical use in the treatment of infections caused by MDR GNRs.

***Meropenem/Vaborbactam***

As a carbapenem, meropenem is inherently resistant to degradation by penicillinases and cephalosporinases. Meropenem also has activity against inherently resistant GNRs such as *P. aeruginosa* and *A. baumanii* [76]. Vaborbactam is a carbapenemase inhibitor with activity against Ambler class A β-lactamases (KPC) and class C β-lactamases (P99, MIR), but it does not exhibit activity against Ambler class B (NDM, VIM, IMP) or class D (OXA-48) β-lactamases [77, 78]. Overall, meropenem/vaborbactam's role in therapy is similar to ceftazidime/avibactam in that the addition of vaborbactam restores the activity of meropenem against *Enterobacteriaceae* that produce KPCs. Unlike ceftazidime/avibactam, the addition of vaborbactam does not improve susceptibility in meropenem-resistant bacteria that produce OXA-48 β-lactamases. Meropenem/vaborbactam is also of limited use in the treatment of MDR *P. aeruginosa,* as the addition of vaborbactam does not affect carbapenem-specific porin channels.

***Plazomicin***

Plazomicin has exhibited activity against *Enterobacteriaceae* isolates, with resistance against gentamicin, tobramycin, and amikacin [79]. This retained activity is due to plazomicin's unique structure, which confers resistance to most aminoglycoside-modifying enzymes (AMEs) that cause aminoglycoside resistance [80]. Plazomicin does not have any unique protection against other mechanisms that confer bacterial resistance to aminoglycosides such as efflux pumps or target site modification. As most strains of MDR *P. aeruginosa* and *A. baumanii* have additional mutations conferring aminoglycoside resistance along with producing aminoglycoside-modifying enzymes, plazomicin often has similar activity against these bacteria as other aminoglycosides [81]. Also, bacteria that produce carbapenemases such as NDM and OXA-type often have modified aminoglycoside target sites that confer resistance to all aminoglycosides, including plazomicin [82]. Despite this, Serio and colleagues showed that 66% of NDM-producing *Enterobacteriaceae*, 89.6% of VIM-producing *Enterobacteriaceae*, and 100% of IMP-producing *Enterobacteriaceae* were susceptible to plazomicin [83]. For susceptible isolates, plazomicin is an option in the treatment of infections caused by metallo-β-lactamase-producing *Enterobacteriaceae*.

***Omadacycline***

Omadacycline is an aminomethylcycline in the tetracycline family of antibiotics with a unique structure that allows it to overcome many tetracycline-specific resistance mechanisms such as efflux pumps and target site protection [84]. Omadacycline does not exhibit activity against *Pseudomonas* spp., but it does inhibit some strains of *A. baumanii* [85]. Omadacycline does carry a warning for increased mortality based on the results of the OPTIC trial, where more patients with community-acquired pneumonia treated with omadacycline (2.1%) than those treated with moxifloxacin (1.0%) died during the trial. The role of omadacycline in the treatment of MDR *Enterobacteriaceae* is currently unclear, but it could see use in the treatment of infections caused by bacteria-producing carbapenemases such as KPCs, NDM, and OXA-48 or by susceptible *A. baumanii* or *Stenotrophomonas maltophillia* [86, 87].

***Eravacycline***

Eravacycline is a fluorocycline in the tetracycline family of antibiotics that is similar to omadacycline in that its unique structure allows it to overcome common tetracycline resistance mechanisms such as ribosomal protection and efflux pumps [88]. Similar to omadacycline, eravacycline has no activity against *Pseudomonas* spp. but does inhibit some strains of *A. baumanii* and carbapenemase-producing *Enterobacteriaceae* [89]. While eravacycline did show noninferiority to ertapenem and meropenem in the treatment of complicated intra-abdominal infections, it was unable to achieve noninferiority compared with levofloxacin in the treatment of complicated urinary tract infections [88]. Overall, eravacycline's role in the treatment of MDR *Enterobacteriaceae* is similar to that of omadacycline: It is an option to treat infections caused by bacteria-producing carbapenemases or susceptible *A. baumanii,* but it may be particularly effective in the treatment of intra-abdominal infections.

***Imipenem/Cilastatin/Relebactam***

Imipenem, much like meropenem, is a carbapenem with a broad spectrum of activity against numerous bacteria including *P. aeruginosa* and *A. baumanii* [76]. Cilastatin is a dehydropeptidase-1 inhibitor that prevents renal metabolism of imipenem to allow for therapeutic concentrations of the antibiotic [90]. Relebactam is similar to avibactam in that it has activity against Ambler class A, C, and some D β-lactamases [91, 92]. As imipenem/cilastatin/relebactam has demonstrated activity against KPC-producing *Enterobacteriaceae*, the addition of relebactam did not restore imipenem's activity against OXA-48-producing bacteria [93]. This is unlike ceftazidime/avibactam, which is active against OXA-48-producing bacteria [69]. The role of imipenem/cilastatin/relebactam in clinical therapy is similar to that of meropenem/vaborbactam. The trio can be considered in the treatment of infections caused by *Enterobacteriaceae* that produce KPCs, but not those that produce OXA-48 or Ambler class B β-lactamases.

*Cefiderocol*

Cefiderocol is unique in that it chelates with ferric iron, which allows it to be brought into GNRs via iron transport systems instead of through passive diffusion via porins like other β-lactams [94, 95]. This unique mechanism allows cefiderocol to overcome resistance conferred by decreased porin expression. While chelated with iron, cefiderocol is also resistant to hydrolysis by all β-lactamases, including Ambler class B [96, 97]. Cefiderocol has also shown in vitro activity against MDR *Stenotrophomonas maltophilia*, MDR *A. baumannii*, and MDR *P. aeruginosa* [98]. Cefiderocol is approved for the treatment of cUTI, but it has a labeled warning for increased mortality based on the results of the CREDIBLE-CR trial [99]. Overall, cefiderocol's primary place in therapy is in the treatment of infections caused by MDR *S. maltophilia*, MDR *A. baumanii*, MDR *P. aeruginosa,* and CRE that produce Ambler class B β-lactamases.

## CONCLUSIONS

The treatment of gram-negative bacterial infections has advanced considerably over the course of the last decade. In this current report, the field has evinced an increasing number of scholarly publications and dissemination as the 2010s progressed. This work identified publication themes of clinical practice that underwent rapid development during the 2010s. These themes included the management of infections caused by MDR GNRs and pulmonary infections in patients with cystic fibrosis. Also, the literature provided information on the declining scholarly interest in combination therapy for the treatment of MDR GNRs, as newer antibiotics have been developed under the GAIN Act. Nine new antibiotics were covered in this literature review, most of which have niche roles in the treatment of MDR gram-negative bacterial infections. The 2010s were a decade of significant scholarship concerning the treatment of gram-negative bacterial infections, which portends further developments in this area of practice in the years to come.

### Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases online*. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.


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