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ANTIMICROBIAL DEVELOPMENT AND DRUG RESISTANCE (A PAKYZ, SECTION EDITOR)

Resistance Trends and Treatment Options in Gram-Negative Ventilator-Associated Pneumonia

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Abstract

Purpose of Review Hospital-acquired and ventilator-associated pneumonia (VAP) are frequent causes of infection among critically ill patients. VAP is the most common hospital-acquired bacterial infection among mechanically ventilated patients. Unfortunately, many of the nosocomial Gram-negative bacteria that cause VAP are increasingly difficult to treat. Additionally, the evolution and dissemination of multi- and pan-drug resistant strains leave clinicians with few treatment options. VAP patients represent a dynamic population at risk for antibiotic failure and under-dosing due to altered antibiotic pharmacokinetic parameters. Since few antibiotic agents have been approved within the last 15 years, and no new agents specifically targeting VAP have been approved to date, it is anticipated that this problem will worsen. Given the public health crisis posed by resistant Gram-negative bacteria, it is essential to establish a firm understanding of the current epidemiology of VAP, the changing trends in Gram-negative resistance in VAP, and the current issues in drug development for Gram-negative bacteria that cause VAP.

Recent Findings Rapid identification technologies and phenotypic methods, new therapeutic strategies, and novel treatment paradigms have evolved in an attempt to improve treatment outcomes for VAP; however, clinical data supporting alternative treatment strategies and adjunctive therapies remain sparse. Importantly, new classes of antimicrobials, novel virulence factor inhibitors, and beta-lactam/beta-lactamase inhibitor combinations are currently in development. Conscientious stewardship of new and emerging therapeutic agents will be needed to ensure they remain effective well into the future.

Keywords Ventilator-associated pneumonia · Gram-negative bacteria epidemiology · Rapid diagnostic technologies · Antibacterial agents · Novel therapeutics · Drug development

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Introduction: Gram-Negative Resistance in VAP

Ventilator-associated pneumonia (VAP) is a devastating nosocomial infection responsible for excessive morbidity and mortality. Attributable mortality in VAP is roughly 9–13%, but higher mortality rates in select populations have been observed [1, 2]. VAP remains a common hospital-acquired bacterial infection among mechanically ventilated patients [3], with management complicated by increasing Gram-negative resistance [4]. The evolution and dissemination of multidrug resistance [5] among Gram-negative bacteria means that for some patients with VAP, no active reliable treatments exist [4, 6]. In this review, we focus on epidemiological trends in VAP, the evolving landscape of Gram-negative resistance, and currently available and emerging treatments options for patients with VAP caused by Gram-negative bacteria.

VAP Epidemiology: Definitions, Surveillance, and Diagnostic Testing

Consensus guidelines define VAP as a pneumonia occurring > 48 h after endotracheal intubation [7]. VAP occurs in between one tenth and one third of mechanically ventilated patients [7] with estimated incidence rates between 1.2 and 8.5 cases per 1000 ventilator days [8]. However, the frequency of VAP has been challenging to measure. No widely accepted diagnostic test for VAP is currently available [9], and reliable definitions remain elusive [10].

Evolving Definitions

Decreasing VAP rates according to the National Healthcare Safety Network (NHSN) were noted between 2006 and 2012 [11, 12]. However, a contemporaneous patient-level analysis revealed stable VAP rates [13]. Correspondingly, the updated VAP surveillance definition now classifies ventilator-associated events using clinical and temporal criteria [10]. While this definition was initially felt to be highly sensitive (93.5%, 95% CI 77.2–98.8%) and specific (100%, 95% CI 98.8–100%) for VAP [14], subsequent studies demonstrated lower operating characteristics and susceptibility to manipulation [15, 16]. Underreporting VAP within the surgical and trauma populations also remains problematic [15, 16]. Reliable VAP definitions applicable to multiple highly variable ICU populations are necessary.

Diagnostic Testing

Improved definitions paired with cutting-edge diagnostics may improve the accuracy of VAP identification. Standard culture-based testing requires specimen inoculation and growth in media, with identification and susceptibility results occurring days later. Molecular methods (i.e., rapid diagnostics) can identify Gram-negative species and detect resistance minutes to hours after specimen collection. The revolution in rapid diagnostics means that near real-time pathogen and resistance identification is possible.

Genotypic Methods

Genotypic tests, like automated real-time multiplex polymerase chain reaction (PCR) and microarray platforms, are examples of emerging diagnostic methods [17, 18]. Curetis Unyvero (Curetis AG) is a multiplex PCR hybridization system designed to identify pneumonia pathogens and resistance genes in respiratory samples [19]. A similar panel is under development for the Biofire platform. Verigene is a nanoparticle-based amplification method for identifying Gram-negative species and resistance genes, but this panel is only Food and Drug Administration (FDA)-approved for positive blood cultures identified using conventional growth detection methods [20]. Ribosomal amplification (e.g., 16S ribosomal RNA gene PCR) has also been evaluated in suspected VAP cases [21, 22].

Phenotypic Methods

Rapid phenotypic methods provide susceptibility or resistance classification and may complement rapid identification methods. The Carba NP test (Biomerieux) directly detects carbapenem hydrolysis and can identify the presence of specific carbapenemases irrespective of species [23]. Automated systems, like the Accelerate Pheno system (Accelerate Diagnostics), provide identification and susceptibility data 1–2 days faster than traditional methods [24].

Other Emerging Methods

Emerging technologies are able to identify Gram-negative bacteria directly from clinical specimens. T2Bacteria (T2Biosystems) utilizes magnetic resonance to identify pathogens directly from blood, but this panel has not been FDA cleared [25]. Deep sequencing technologies have also recently been applied to clinical specimens.

Epidemiology of Gram-Negative VAP Pathogens

Gram-negative VAP pathogens are increasingly antibiotic resistant [4, 26]. National and international surveillance databases (e.g., NHSN, INFORM, SENTRY) document the dissemination of Gram-negative resistance [26–28]. For example, up to 40% of select Gram-negatives in the USA exhibit multi-drug resistance (MDR) [5], suggesting that broad empiric therapy may be required. Recent trials also provide Gram-negative recovery and susceptibility rates. In the following section, we review trends from surveillance databases and clinical trials.

Recent Trends in Gram-Negative Rates

Gram-negative recovery in VAP varies globally; yet, specific pathogens are consistently recovered. *Pseudomonas aeruginosa*, *Acinetobacter* spp., and *Enterobacteriaceae* have been frequently implicated [9, 26–28]. Surveillance recovery rates are summarized in Table 1. Here, we review Gram-negative rates in nosocomial pneumonia.

P. aeruginosa

P. aeruginosa is the preeminent and most common Gram-negative nosocomial pneumonia and VAP pathogen in the

Table 1 Prevalence of Gram-negative VAP pathogens from nosocomial pneumonia surveillance studies

		NHSN[27]	INFORM[28]		SENTRY		
Gram-negative groups	Year Location	2011–2012 USA	2011–2015 USA	2015 USA	2012[29] USA	2009–2012[26] USA	2009–2012[26] Europe and Mediterranean region
Non-fermenting bacteria	*Pseudomonas aeruginosa*	16.50%	39.56%[a]	22.70%	29.20%	20.90%[b]	20.90%[b]
	Acinetobacter spp.	6.10%	3.71% [a]	3.30%	2.70%	3.70%[b]	7.50%[b]
	Stenotrophomonas spp.	3.90%	NR	NR	4.70%	4.40%[b]	3.20%[b]
Enterobacteriaceae	*Citrobacter* spp.	0.70%	1.81%[a]	NR	NR	NR	NR
	Escherichia coli	5.40%	12.00%[a]	9.00%	5.50%	5.50%[b]	11.80%[b]
	Enterobacter spp.	8.30%	13.82%[a]	6.80%	7.70%	5.90%[b]	5.50%[b]
	Klebsiella spp.	10.20%	18.68%[a]	11.80%	10%	9.70%[b]	11.60%[b]
	Serratia spp.	4.60%	8.10%[a]	4.40%	5.90%	3.80%[b]	4.00%[b]

NR not reported

[a] Percent of Gram-negatives in VAP

[b] Percent of patients hospitalized with pneumonia

USA, as confirmed in multiple studies (Table 1) [26–28, 30]. European clinical studies also support the prominent role of *P. aeruginosa* in VAP (14–19% of cases) [31, 32].

Acinetobacter baumannii

A. baumannii ranks among the top five VAP pathogens worldwide. NHSN surveillance identified *A. baumannii* as the fifth most common VAP pathogen in the USA and Europe, accounting for 6.1 to 7.5% of VAP cases (Table 1) [26, 27]. However, only 2.7 and 3.3% of US VAP isolates were *A. baumannii* in the SENTRY and INFORM databases, respectively [28, 30]. The prevalence of *A. baumannii* within Asian countries was slightly higher than US and European rates [33, 34].

Enterobacteriaceae

Members of the *Enterobacteriaceae* genus have also been frequently recovered in VAP; four of the top ten Gram-negative VAP pathogens are *Enterobacteriaceae* [27]. *K. pneumoniae* and *Enterobacter* spp. were identified in 10.2 and 8.3% of VAP cases by NHSN surveillance [27] and contributed 10.0 and 7.7% of VAP cases, respectively, within SENTRY [30]. INFORM found slightly higher rates of *K. pneumoniae* and *Enterobacter* spp. among Gram-negative VAP cases (Table 1) [28]. *E. coli* and *Serratia* spp. are also among the top ten VAP pathogens [26, 28, 30]. Within the European and Mediterranean regions, *Enterobacteriaceae* were also common [26] and increasing in frequency [35]. *E. coli* was the most common European pathogen. *Klebsiella* spp. were responsible for a similar proportion of infections in Europe and the USA (11.6 vs. 9.7%) (Table 1).

Recent Trends in Gram-Negative Resistance

Gram-negative resistance has become a global crisis. Among Gram-negative VAP pathogens, multidrug resistance and resistance to last-line agents (e.g., colistin) is alarmingly common. Resistance among *P. aeruginosa* and *A. baumannii* has become the norm, while carbapenem resistance among *Enterobacteriaceae* has emerged as an imminent threat to global health [4, 36]. In the following section, we review Gram-negative VAP pathogen resistance trends using Clinical and Laboratory Standards Institute definitions (2010–present).

P. aeruginosa Resistance

P. aeruginosa has the capacity to develop resistance to all VAP antibiotics. Carbapenem resistance has been documented in 16.1–28.4% of US nosocomial pneumonia isolates [26–28, 30]. Among VAP isolates, *P. aeruginosa* resistance to anti-pseudomonal penicillins (e.g., piperacillin-tazobactam, 15.6–19.1%) and anti-pseudomonal cephalosporins (e.g., ceftazidime or cefepime, 9.5–29.4%) is increasingly common [26–28, 30]. The aminoglycosides tobramycin and amikacin appear to retain good individual activity against *P. aeruginosa* in some studies (> 90% susceptible) [26, 28]. However, resistance to ≥ 1 aminoglycoside (e.g., amikacin or gentamicin or

tobramycin) is increasingly common among VAP isolates (18.2–23.3% resistant) [27]. Colistin remains active against *P. aeruginosa* (98–99.6% susceptible) [26, 28]. Resistance among European and Mediterranean isolates was also common. With the exception of colistin, European isolates were more likely than US isolates to exhibit resistance [26]. Beta-lactam resistance among *P. aeruginosa* respiratory isolates is alarmingly common, while aminoglycosides and colistin remain fairly active.

A. baumannii Resistance

A. baumannii is frequently MDR and often carbapenem resistant. Over 50% of US *A. baumannii* VAP isolates were MDR, and up to 64% of isolates exhibited carbapenem resistance (55.5–63.5%) [26, 27]. With resistance rates less than 5%, colistin appears active against *A. baumannii* [26]. Resistance to minocycline was found in 14.8% of isolates, and tigecycline MICs exceeding the FDA *Enterobacteriaceae* breakpoint [37] were found in 1.6% of isolates [26]. European and Mediterranean *A. baumannii* pneumonia isolates demonstrated similar resistance patterns, with slightly higher meropenem and minocycline resistance (67.1 and 22.2%, respectively) [26]. Few VAP agents have reliable activity against *A. baumannii*. Colistin, minocycline, and tigecycline may retain activity, but susceptibility testing is essential.

Enterobacteriaceae Resistance

Resistance among *Enterobacteriaceae* is particularly concerning and often varies by genera. In the USA, cefepime or ceftazidime resistance varies widely (2.7–30%) [26, 27]. Carbapenem resistance in *E. coli* and *Enterobacter* spp. remains relatively low (0.5–2.2% and 1–3.2%, respectively) [26–28]. *Klebsiella* spp. have demonstrably higher carbapenem-resistance rates (6.9–11.5%) [26–28]. European and Mediterranean *Enterobacteriaceae* were more likely to exhibit MDR and to carry genes encoding extended-spectrum beta-lactamases (ESBLs) [26]. Similar to the US, carbapenem resistance among *Klebsiella* spp. was common [26]. Carbapenem-resistant *Enterobacteriaceae* (CRE) were found in 58 centers in 18 European countries, comprising 2% of all *Enterobacteriaceae*; however, large inter-country variability exists [30]. Cases of colistin-resistant *mcr-1*-carrying *Enterobacteriaceae* infections have been documented in the USA, Europe, and Asia [38–40]. The global dissemination of CRE and *mcr-1*-carrying isolates has significantly impacted the management of VAP patients, leaving clinicians with few or no safe and effective treatments.

Contemporary Treatment Strategies for Gram-Negative VAP

While new therapeutic agents and novel treatment approaches are currently being investigated, clinicians caring for patients with Gram-negative VAP are caught between two opposing forces: increasing resistance on one hand and a dwindling antibiotic armamentarium on the other. In the following section, we describe new antibiotics, new uses of older antibiotics, and novel strategies for Gram-negative VAP pathogens.

Agents for the Treatment of VAP Caused by MDR Gram-Negative Bacteria

The increasing frequency with which MDR Gram-negative bacteria cause VAP has forced clinicians and pharmaceutical companies to become more creative. Old antibiotics have been recycled, established antibiotics have been used in new ways, new antibiotics have been developed, and entirely novel therapeutic strategies are being investigated (Table 2).

Renaissance Antibiotics

Antimicrobial resistance has become so pervasive and extreme that formerly discarded antibiotics are being recycled in attempts to find agents that retain activity against MDR bacteria. Some of these "renaissance antibiotics" now play an important role in clinical practice.

Fosfomycin Fosfomycin is a derivative of phosphonic acid that blocks an early stage in the synthesis of peptidoglycan, a component of the bacterial cell wall [41]. First discovered in 1969 [42], fosfomycin has recently received renewed interest for MDR Gram-negative bacteria. Approximately three fourths of carbapenem-resistant *K. pneumoniae* isolates are susceptible to fosfomycin [43]. However, fosfomycin monotherapy is less active against *P. aeruginosa* and *A. baumannii*, with resistance emerging rapidly [44]. Although not currently available in the USA, intravenous fosfomycin penetrates the lung well, and limited data suggest it may be efficacious in this setting [45].

Polymyxins First used in the 1950s, systemic polymyxins [B and E (i.e., colistin)] were abandoned by the early 1980s due to toxicity and availability of safer alternatives. In recent years, they have re-emerged for the treatment of MDR Gram-negative bacteria, including *P. aeruginosa*, *Acinetobacter* spp., *E. coli*, and *Klebsiella* spp. However polymyxins lack activity against some other Gram-negatives, such as *Proteus* and *Serratia* spp. Susceptibility notwithstanding, polymyxins suffer from two disadvantages. High-dose systemic polymyxin regimens that are necessary for serious infections like VAP have been associated with renal toxicity

Table 2 Summary of emerging therapeutic options and treatment strategies related to Gram-negative VAP

Therapeutic paradigm in VAP	Specific agent or approach	FDA approval status	Advantages	Limitations
Renaissance antibiotics	Fosfomycin	Approved: 1996 Availability: oral	Active against some CRE and ESBL-producing organisms	• Low activity against PA or AB • Oral form approved for uncomplicated UTI only • IV formulation pending approval • Nebulization being studied
	Polymyxin B and polymyxin E (colistin)	Approved: use prior to 1962* Availability: IV and inhaled	Active against some AB, CRE, ESBL-producing organisms, and PA	• Little to no activity against *Proteus* or *Serratia* spp. • Optimal dosing for VAP unclear • Nephrotoxic
	Minocycline	Approved:1982 Availability: IV and oral	Active against some AB, CRE, and ESBL-producing organisms Concentrations higher than tigecycline	• Low in vitro activity against PA, *Proteus*, and *Serratia* spp. • Low achievable concentrations • Variable AB susceptibility
New antibiotics	Tigecycline	Approved: 2005 Availability: IV	Active against some AB, some CRE, and some ESBL-producing organisms Lung ELF ratio for tigecycline ~ 130–170%	• Lower clinical response vs. imipenem • Higher all-cause mortality in VAP • Lower in vitro activity against PA, *Proteus*, and *Providencia* spp. • Low achievable concentrations
	Doripenem	Approved: 2007 Availability: IV	Active against some ESBL-producing organisms, and some PA Lung ELF ratio for doripenem ~ 28%	• Lower clinical response vs. imipenem • Optimal dosing for VAP unclear
	Ceftobiprole	Application rejected: 2009 Availability: IV	Active against Gram-positives, Gram-negatives, and some PA Lung ELF ratio for the two agents ~ 69%	• Lower efficacy in VAP vs. ceftazidime/linezolid • Lower clinical cure and eradication rates vs. AB and PA • Optimal dosing for VAP unclear
	Ceftazidime-avibactam	Approved: 2014 Availability: IV	Active against some CRE, some ESBL-producing organisms, and some PA Lung ELF ratio for the two agents ~ 32%	• Efficacy in VAP not yet known • Optimal dosing for VAP unclear • Lower in vitro activity against AB and SM
	Ceftolozane-tazobactam	Approved: 2015 Availability: IV	Active against some MDR PA and some ESBL-producing organisms Lung ELF ratio for ceftolozane ~ 48%	• Efficacy in VAP not yet known • Optimal dosing for VAP unclear • Clinical activity against ESBL-producing organisms unclear • Lower in vitro activity against AB and SM
	Meropenem-vaborbactam	Approved: 2017 Availability: IV	Active against CRE and some ESBL-producing organisms Lung ELF ratio for the two agents ~ 65–79%	• Efficacy in VAP not yet known • Optimal dosing for VAP unclear • Lower in vitro activity against AB and SM
	Imipenem-cilastatin/relebactam	In clinical trials Availability: IV	Active against some CRE and ESBL-producing organisms	• Efficacy in VAP not yet known • Optimal dosing for VAP unclear • Lower in vitro activity against AB, PA, and SM
	Plazomicin	In clinical trials Availability: IV	Active against some AB, CRE, ESBL-producing organisms, and PA Lung ELF ratio for plazomicin ~ 13%	• Efficacy in VAP not yet known • Optimal dosing for VAP unclear

Table 2 (continued)

Therapeutic paradigm in VAP	Specific agent or approach	FDA approval status	Advantages	Limitations
				• Ribosomal methyltransferases may reduce activity against certain strains
	Eravacycline	In clinical trials Availability: oral and IV	Active against Gram-negatives including AB, CRE, ESBL-, and NDM-producing organisms Lung ELF ratio for eravacycline ~ 644%	• Efficacy in VAP not yet known • Optimal dosing for VAP unclear • Lower activity vs. PA compared to AB and SM
New strategies	Cefiderocol	In clinical trials	Active against some AB, CRE, PA, and SM Unique mechanism of outer membrane penetration	• Efficacy in VAP not yet known • Optimal dosing for VAP unclear
	MEDI3902	In clinical trials	Active against the type III secretion needle complex of PA Unique monoclonal antibody that may protect against acute infection	• Efficacy in VAP prevention not yet known • Optimal dose to prevent VAP unclear • Single indication of prevention and only activity against PA
New tactics	Inhaled antibiotic combination therapy	Many available agents: tobramycin, gentamicin, amikacin, colistin, polymyxin B	Activity against broad range of pathogens High target site concentrations achieved Potential increase in clinical cure, mostly driven by inhaled colistin	• No consistent evidence of reduced mortality or eradication with inhaled combination therapy in VAP
	Adjunctive macrolide use	Available but not approved for VAP: Clarithromycin Azithromycin Erythromycin	Immune and inflammatory modulation Earlier resolution and weaning from mechanical ventilation and lower 90-day mortality with clarithromycin	• Limited clinical data • No in vitro activity against majority of Gram-negative VAP pathogens
	Prolonged infusion beta-lactams	Extended infusion over 3–4 h Continuous infusion over 24 h	Increases beta-lactam T > MIC Continuous infusion associated with greater clinical cure and lower mortality in meta-analyses	• Variability in treatment outcomes with extended and continuous infusion versus traditional dosing • Few VAP-specific studies available
	Modification of total treatment duration	Short: 3–5 days Standard: 7–8 days Long: 10–14 days	Meta-analyses suggest lower recurrence with longer durations for some Gram-negatives	• Meta-analyses found no difference in 28-day mortality with longer durations

VAP ventilator-associated pneumonia, *FDA* Food and Drug Administration, *CRE* carbapenem-resistant *Enterobacteriaceae*, *ESBL* extended spectrum β-lactamase, *PA Pseudomonas aeruginosa*, *AB Acinetobacter baumannii*, *SM Stenotrophomonas maltophilia*, *UTI* urinary tract infection, *IV* intravenous, *ELF* epithelial lining fluid, *MDR* multidrug-resistant, *NDM* New Delhi metallo-β-lactamase, *T > MIC* time above the minimum inhibitory concentration

* Antibiotic approved by the FDA and used clinically prior to Kefauver Harris Amendment in 1962 requiring efficacy and safety for approval

rates of 20% or more [46], and cure rates with monotherapy are low [47]. Thus, current VAP guidelines suggest avoiding systemic polymyxins when alternatives exist [9].

Minocycline Minocycline, an FDA-approved semisynthetic tetracycline derivative first developed in the 1960s [48], has only recently been used for MDR Gram-negative VAP [49]. Like tigecycline, minocycline has Gram-negative activity [50] but yields higher blood levels than tigecycline [51]. Minocycline is active against some *Acinetobacter* and *Stenotrophomonas* spp. and some *Enterobacteriaceae* but not *Serratia* spp., *Proteus* spp., or *P. aeruginosa* [50]. Minocycline has garnered interest for MDR *A. baumannii* VAP, with a number of clinical responses reported across 23 cases [49]. Though controlled VAP trials are lacking, minocycline exhibits good lung penetration [measured by the epithelial lining fluid to serum (ELF/serum) AUC ratio ~2.5] and *A. baumannii* killing in a mouse model [52].

New Antibiotics

Approved Antibiotics

Tigecycline Tigecycline, a glycylcycline antibiotic approved by the FDA in 2005, has broad Gram-negative activity including some CRE [30] but not *P. aeruginosa* or *Proteus mirabilis*. In a randomized controlled trial of 945 people with HAP/VAP, tigecycline was associated with lower response rates than imipenem [53]. Tigecycline was also associated with excess mortality in several studies [54–56], driven primarily by patients with nosocomial pneumonia. For these reasons, tigecycline should primarily be used as a component of combination therapy [9].

Doripenem Doripenem, a carbapenem approved by the FDA in 2007, initially showed promise for treatment of patients with Gram-negative VAP [57]. In vitro testing showed slightly lower MICs against *P. aeruginosa* compared to other carbapenems [58]. However, a subsequent study of 274 patients with Gram-negative VAP randomly assigned to receive a 7-day course of doripenem or a 10-day course of imipenem-cilastatin was stopped prematurely due to a lower cure rate (45.6 vs. 56.8%; 95% CI, −26.3 to 3.8%) and higher all-cause 28-day mortality (21.5 vs. 14.8%; 95% CI, −5.0 to 18.5) in the doripenem treatment arm [59]. As a result, current VAP guidelines do not recommend the use of doripenem [9].

Ceftazidime-Avibactam Unlike other approved beta-lactamase inhibitors, avibactam is not a beta-lactam but does bind beta-lactamases. Ceftazidime-avibactam has enhanced activity against *Enterobacteriaceae* (including ceftazidime-resistant strains) and *P. aeruginosa*. Arguably, the most useful aspect of this antibiotic is its ability to inhibit ESBLs, AmpC beta-lactamases, and serine carbapenemases [60]. However, metallo-beta-lactamases (e.g., IMP, VIM, NDM) are not inhibited by avibactam [60]. Accordingly, ceftazidime-avibactam has good activity against *Enterobacteriaceae* and *P. aeruginosa,* but not *Acinetobacter* and *Stenotrophomonas* spp. A phase III non-inferiority nosocomial pneumonia trial [61] found that ceftazidime-avibactam was non-inferior to meropenem with respect to 28-day mortality [risk difference (RD) 1.5%; 95% CI −2.4-5.3] and cure [RD 1.9%; 95% CI −8.1-4.3] without the emergence of resistance [62]. Of concern, though, are numerous reports of resistance to this agent are already appearing [63–65] including treatment-emergent resistance [66].

Ceftolozane-Tazobactam Whereas ceftazidime-avibactam combines an old cephalosporin with a novel beta-lactamase inhibitor, ceftolozane-tazobactam combines an old beta-lactamase inhibitor with a novel cephalosporin. Ceftolozane has features of ceftazidime but has a bulkier side chain, which prevents cleavage by AmpC beta-lactamases [67], enhancing activity against *P. aeruginosa*. The combination also appears to have activity against non-CRE ESBL-producing *Enterobacteriaceae* [68, 69]. Like ceftazidime-avibactam, ceftolozane-tazobactam has little activity against *A. baumannii* and *Stenotrophomonas* spp. [60]. The ELF/serum AUC ratio for ceftolozane was approximately 50% [70, 71•], indicating a potential role in VAP. The efficacy of ceftolozane-tazobactam in VAP is currently being studied (NCT02070757).

Meropenem-Vaborbactam Meropenem-vaborbactam was approved by the FDA in 2017. Vaborbactam is a boronic acid serine β-lactamase inhibitor with activity against ESBLs, AmpCs, and serine carbapenemases but not metallo-beta-lactamases. Meropenem-vaborbactam has broad activity against *E. coli*, *K. pneumoniae*, and *Enterobacter* spp., including ESBL and CRE isolates, but activity against non-fermenting Gram-negatives is similar to meropenem alone [72]. The TANGO-2 phase III clinical trial of meropenem-vaborbactam for the treatment of infections of the lung, blood, urinary tract, and abdomen was stopped prematurely following enrollment of 72 patients (43 had confirmed CRE), because the interim analysis showed a statistically significant difference in clinical cure favoring meropenem-vaborbactam over best available therapy for patients with CRE [73]. Mortality rates were also lower in patients treated with meropenem-vaborbactam. Both meropenem and vaborbactam achieve ≥ 65% ELF/serum AUC ratios in healthy adults, suggestive of activity in HAP and VAP [74]. However, pharmacokinetic data from patients with VAP indicate that meropenem ELF/serum AUC ratios may be lower (median < 30%) and highly variable [75]. The efficacy of

meropenem-vaborbactam in HAP and VAP is currently being studied (NCT03006679).

Ceftobiprole Ceftobiprole, a cephalosporin broadly active against Gram-positives and Gram-negatives including *P. aeruginosa*, is approved in several European countries but not the USA. A recent phase III trial of 781 patients found ceftobiprole to be equivalent to linezolid plus ceftazidime in the clinical cure of HAP but perhaps inferior among VAP patients [76]. Additional studies are necessary to evaluate the effectiveness of ceftobiprole in VAP.

Antibiotics in Clinical Trials

Imipenem-Cilastatin/Relebactam Relebactam is a non-β-lactam inhibitor of β-lactamases with structural similarity to avibactam. It too has good activity against ESBLs, AmpCs, and serine carbapenemases but not metallo-beta-lactamases [77, 78]. Relebactam extends imipenem's spectrum to include otherwise resistant *E. coli*, *K. pneumoniae*, and *Enterobacter* spp. strains. Relebactam's activity against non-fermenting Gram-negative bacteria such as *P. aeruginosa*, *A. baumannii*, and *S. maltophilia* appears more limited [78]. Both imipenem and relebactam showed good lung penetration, suggesting potential efficacy in VAP [79]. Phase III clinical trials of imipenem-cilastatin/relebactam vs. imipenem-cilastatin or piperacillin/tazobactam in HAP and VAP are underway [80, 81].

Plazomicin Plazomicin, an aminoglycoside derivative, avoids modification and inactivation by many of the enzymes that typically cause aminoglycoside resistance [82]. Plazomicin does not inhibit bacteria that express ribosomal methyltransferases (e.g., 16s rRNA methylases) [83]. Plazomicin has good activity against MDR *Enterobacteriaceae*, including ESBL and serine carbapenemase producers. Against *P. aeruginosa* and *A. baumannii,* plazomicin may be more active than amikacin [84]. In a phase III trial (CARE) studying nosocomial pneumonia caused by CRE, plazomicin exhibited a mortality benefit relative to colistin when both agents were used with either meropenem or tigecycline [85]. The efficacy of plazomicin for the treatment of VAP is unknown, and the ELF/serum AUC ratio was ~ 13% [83]. Of note, plazomicin's renal toxicity profile appeared favorable compared with colistin [86, 87].

Eravacycline Eravacycline has structural similarity to tigecycline and also acts by binding the ribosome to inhibit protein synthesis [88]. It has broad activity against aerobic and facultative Gram-positive and Gram-negative bacteria. Eravacycline has potent activity against *Enterobacteriaceae*, including ESBL-, KPC-, and NDM-producing isolates [89, 90]. Compared to tigecycline, eravacycline exhibited modestly lower MICs against *A. baumannii* and *S. maltophilia* but no enhanced activity against *P. aeruginosa* [89, 90]. One potential advantage of eravacycline is the availability of an oral formulation. In the phase III IGNITE1 and IGNITE4 clinical trials twice daily IV eravacycline was non-inferior to ertapenem or meropenem among patients with complicated intra-abdominal infections [91, 92]. In a phase III (IGNITE2) clinical trial of hospitalized patients with complicated urinary tract infections, eravacycline was inferior to levofloxacin [93]; however, patients receiving IV eravacycline responded better than those receiving oral eravacycline. The role of eravacycline in VAP is currently unclear.

New Tactics: Unconventional Uses of Existing Agents

Another approach to treating patients with VAP caused by MDR bacteria is to use currently approved antibiotics in new ways to enhance efficacy.

Inhaled Antibiotics Aerosolized administration of antibiotics has the theoretical advantage of achieving high local concentrations of antimicrobial agents in the lungs, perhaps even exceeding the MICs of resistant Gram-negative bacteria. A meta-analysis of a randomized controlled trial and observational studies (437 total patients) examined the use of adjunctive nebulized antibiotics in MDR VAP and showed significantly higher clinical resolution among patients receiving nebulization (OR 1.96; 95% CI 1.30–2.96) [94]. Nebulization has been used with the following Gram-negative antibiotics: gentamicin, tobramycin, amikacin, aztreonam, ceftazidime, and colistin [95]. Current guidelines recommend adjunctive inhaled antibiotics for the treatment of VAP caused by Gram-negative bacteria susceptible to only aminoglycosides or polymyxins.

Macrolides Macrolides do not exhibit in vitro activity against most Gram-negative VAP pathogens. Yet, these agents can produce potentially beneficial immunomodulatory changes in pneumonia. A multicenter, double-blinded study of 200 ICU patients with sepsis and VAP found that adjunctive clarithromycin led to earlier VAP resolution and faster mechanical ventilation weaning [96, 97].

Prolonged Infusions of Beta-Lactams Prolonged infusion (PI) dosing of beta-lactams includes extended infusion (3–4 h; EI) and continuous infusion (24 h; CI) dosing. VAP clinical cure was greater [98, 99], but mortality was similar with PI piperacillin-tazobactam versus standard infusion [98–100]. VAP clinical cure was also higher with PI ceftazidime (89 vs. 52%: $P < 0.001$) and PI meropenem (90 vs. 60%: $P < 0.001$) versus standard infusion [101, 102]. Randomized trials have evaluated CI vs. standard infusion [103–105]. CI-treated patients had a lower risk of mortality (RR 0.74; 95% CI 0.56–

1.00; $P = 0.045$) and a greater chance of clinical cure (RR 1.2; 95% CI 1.03–1.40; $P = 0.021$) in a patient-level meta-analysis of three trials [106••]. The majority of patients had a respiratory source of infection (55%) [106••]. Until high-quality trials evaluating VAP outcomes are available, PI dosing appears reasonable [9].

Standard Versus Long Treatment Durations Several studies have compared the clinical efficacy of standard (≤ 8 days) versus long (> 8 days) treatment durations [59, 107, 108•, 109–111]. A systematic review and meta-analysis failed to identify a benefit of long durations on 28-day mortality (n = 3 studies; OR = 1.18, 95% CI 0.77–1.8), 28-day mortality among patients with non-fermenting Gram-negatives (n = 2 studies; OR = 0.95, 95% CI 0.39–2.27), or overall pneumonia recurrence (n = 19 studies; OR = 1.41, 95% CI 0.94–2.12) [112]. In the subset of patients with non-fermenting Gram-negatives, the risk of recurrence favored a long duration (n = 2 studies; OR = 2.18. 95% CI 1.14–4.16) [112]. A randomized, open-label, non-inferiority study (iDIAPASON) will compare 8 versus 15 days for *P. aeruginosa* VAP specifically [113]. The shortest effective duration of VAP treatment also remains unclear. Recent (NCT00410527, NCT01554657) and ongoing (NCT01994980) trials will evaluate short (i.e., 3–5 days) durations. Currently, 7- to 8-day durations are reasonable for improving patients [9].

Novel Strategies

Perhaps predictably, the pressures on the conventional antibiotic pipeline have led to efforts to use unconventional approaches to treat MDR Gram-negatives. Here, we briefly discuss several examples.

Cefiderocol Cefiderocol is a siderophore-cephalosporin conjugate that works as a "Trojan horse." It binds iron and then uses the bacterium's iron uptake system to penetrate the outer membrane [114]. In so doing, it overcomes multiple resistance mechanisms (e.g., porin channel deletion, efflux pump overexpression) while localizing the cephalosporin within the periplasm, adjacent to PBPs. Cefiderocol has in vitro activity against many Gram-negative bacteria, including CRE, *P. aeruginosa*, *A. baumannii*, and *S. maltophilia.* In a study of 753 MDR clinical isolates, including carbapenemase- and ESBL-producing bacteria, cefiderocol had superior in vitro activity to meropenem, ceftazidime, and ceftazidime-avibactam and equivalent activity to colistin and tigecycline [115]. A clinical trial for the treatment of nosocomial pneumonias comparing cefiderocol to meropenem, each in combination with linezolid, is underway (NCT03032380).

Anti-Virulence Therapies Disabling a bacterium's virulence factors may prevent it from damaging tissues and make it vulnerable to clearance by the host immune system. Such approaches are not new; antibody-containing serum that bound and inactivated diphtheria toxin was used in the 1800s [116]. Advanced agents currently under development are inhibitors of type III secretion systems [117], complex multi-protein needle-like apparatuses used by some Gram-negative bacteria to intoxicate human cells. MEDI3902 (AstraZeneca) is a chimeric bispecific monoclonal antibody that recognizes both the tip of the *P. aeruginosa* type III secretion needle and surface polysaccharide Psl [118]. The presence of both antigen-binding sites confers synergistic protection against *P. aeruginosa* in animal models [118]. A phase II clinical trial examining the efficacy of MEDI3902 in preventing *P. aeruginosa* pneumonia among mechanically ventilated patients is currently enrolling patients. Additional antibody therapeutics (e.g., Aerubumab, Adiris Pharmaceuticals) are in development and entering clinical trials (NCT03027609).

Quorum-Sensing Inhibition Quorum sensing (QS) is a cell density-dependent communication system that utilizes signaling molecules (auto-inducers) to regulate virulence in many bacteria. Several natural and engineered compounds block quorum-sensing by preventing the synthesis of auto-inducers or by blocking auto-inducer receptor binding [119] and have shown efficacy in mouse models [120, 121].

Biofilm Prevention Endotracheal tube biofilms are thought to play an important role in VAP. Biofilm eradication can be difficult, in part, because biofilm-forming bacteria can persist in the presence of antibiotics and a robust immune response [122, 123]. Endotracheal tubes coated with silver may prevent or delay development of biofilms and VAP [124].

Phage Therapy Phages (viruses that infect bacteria) specifically target an individual bacterial species or strain, do not infect human cells, and have little or no effect on normal microbial flora. However, the development of resistance, neutralizing host immune responses, and formulation and stability issues are concerns [125]. Phages are exquisitely specific, so phage cocktails are required to target multiple species or strains within a species. Such cocktails showed promise in phase I/II clinical studies against *P. aeruginosa*-mediated chronic otitis [126]. Recent anecdotal reports suggest efficacy in humans against MDR *P. aeruginosa* and *A. baumannii* [127, 128].

Other Strategies Host-directed therapies [129], microbiome alterations (e.g., probiotics) [130], nanotechnology [131], endolysins [132], and bacteriocins [133] have all been investigated as novel treatments for bacterial infections.

Summary

Gram-negative bacteria appear poised to win the antibiotic resistance war. The pace of the development and spread of MDR strains has outstripped the medical community's ability to develop novel antimicrobial agents. However, the number and breadth of new and exciting approaches currently being explored is reason for hope that the balance will soon shift. The results of preclinical, clinical, and epidemiological studies over the coming years will demonstrate whether these new approaches will indeed fulfill their promise and provide clinicians with effective treatments for VAP patients.

Compliance with Ethical Standards

Conflict of Interest NJR: discloses reciept of travel expenses and honoria from American Society of Healthsystem Pharmacists

CC: no relevant disclosures

JNO: no relevant disclosures

RGW: discloses reciept of payment for continuing medical education from Medscape and consulting fees from Meiji-Seiko, Merck, Nabriva, Polyphor, Roche/Genetech, Shionogi, The Medicines Company, Accelerate Diagnostics, Curetis, and bioMerieux

ARH: discloses board membership with Microbiotix, NIH grant funding, travel funds and expenses from Cystic Fibrosis Foundation and American Society of Microbiology, and consulting fees from MedImmune

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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