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MINIREVIEW

New Treatment Options against Carbapenem-Resistant *Acinetobacter baumannii* Infections

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ABSTRACT Carbapenem-resistant *Acinetobacter baumannii* (CRAB) is a perilous nosocomial pathogen causing substantial morbidity and mortality. Current treatment options for CRAB are limited and suffer from pharmacokinetic limitations, such as high toxicity and low plasma levels. As a result, CRAB is declared as the top priority pathogen by the World Health Organization for the investment in new drugs. This urgent need for new therapies, in combination with faster FDA approval process, accelerated new drug development and placed several drug candidates in the pipeline. This article reviews available information about the new drugs and other therapeutic options focusing on agents in clinical or late-stage preclinical studies for the treatment of CRAB, and it evaluates their expected benefits and potential shortcomings.

KEYWORDS *Acinetobacter*, cefiderocol

Acinetobacter baumannii has evolved as a significant hospital pathogen by its ability to resist desiccation, disinfectants, and major antimicrobials (1). Today, a substantial proportion of these isolates are carbapenem-resistant *A. baumannii* (CRAB), i.e., extensively drug-resistant (XDR) or pandrug-resistant (PDR) *A. baumannii* (2). Carbapenem resistance rates exceed 90% in some parts of the world (3), and mortality rates for the most common CRAB infections, i.e., hospital-acquired pneumonia (HAP) and bloodstream infections (BSI), may approach 60% (4). This is significantly higher than rates for carbapenem-susceptible *A. baumannii* infections (5). Current antimicrobials for CRAB (i.e., polymyxins, tigecycline, and sometimes aminoglycosides) are far from perfect therapeutic options due to their pharmacokinetic properties and increasing resistance rates.

In these dire circumstances, the need for new therapeutic options for the treatment of CRAB infections is indisputable. Since antimicrobial discovery and resistance development to the new antimicrobial are nearly simultaneous, drugs with novel mechanisms of action that will overcome current resistance mechanisms are sought after. Currently, there are a small number of drug candidates and other therapeutic options that may meet those expectations. This review will focus on such drugs that are in clinical or late preclinical studies (Table 1). In addition, phage therapy and monoclonal antibodies for CRAB will be evaluated. The purpose of this review is to describe the state of anti-CRAB therapies by providing an overall picture of the current pipeline. As all antimicrobials face the eventual fate of being defeated by the bacteria, possible resistance mechanisms against new therapies will also be evaluated. This review is expected to guide the development of new and better drugs and to inspire further novel therapeutic options against resistant microorganisms.

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TABLE 1 New therapeutic options

Drug	Preclinical	Phase I	Phase II	Phase III	FDA approved
Siderophore cephalosporins					
Cefiderocol	✓	✓	✓	✓	-
Others					
GSK-3342830	✓	-[a]	-	-	-
Fimsbactin plus daptomycin	✓	-	-	-	-
GT-1	✓	-	-	-	-
Tetracyclines					
Eravacycline	✓	✓	✓	✓	✓
TP-6076	✓	✓	-	-	-
New non-β-lactam–β-lactamase inhibitors paired with existing β-lactam antibiotics					
ETX2514 plus sulbactam	✓	✓	✓	-	-
WCK 4234 plus meropenem (WCK-5999)	✓	-	-	-	-
LN-1-255 plus meropenem-imipenem	✓	-	-	-	-
VNRX-5113 (partner β-lactam unspecified)	✓	✓	-	-	-
WCK 5153 plus sulbactam	✓	-	-	-	-
Zidebactam plus cefepime	✓	✓	-	-	-
New β-lactam antibiotics					
AIC-499 (partner β-lactam inhibitor unspecified)	✓	✓	-	-	-
FSI-1671 plus sulbactam	✓		-	-	-
Polymyxin B-derived molecules					
SPR741	✓	✓	-	-	-
FADDI-287	✓	-	-	-	-
Aminoglycosides					
Apramycin	✓	-	-	-	-
Other drug candidates					
LpxC inhibitors	✓	-	-	-	-
RX-P873	✓	-	-	-	-
Other therapeutic options					
Bacteriophage therapy	✓	✓	✓	✓	-
Monoclonal antibodies					
C8	✓	-	-	-	-
AR-401	✓	-	-	-	-

[a]-, terminated and under review.

LIMITATIONS OF CURRENT THERAPEUTIC OPTIONS

Polymyxins, discovered in the 1950s and abandoned in the 1980s due to their toxicity profile and availability of cephalosporins and carbapenems, are currently in use as first-line antimicrobials against CRAB, alone or in combination with other drugs. Polymyxins generally have potent *in vitro* activity against *A. baumannii* strains; however, they suffer from a lack of clinically relevant susceptibility breakpoints, very narrow therapeutic spectrum, and serious side effects of nephrotoxicity and neurotoxicity (6). Resistance emerging during therapy due to colistin-heteroresistant strains and difficulty in determining heteroresistance are other important issues that may result in unfavorable clinical outcomes (7). With an undefined optimal dosing, high toxicity, and increasing resistance (7–9), polymyxin-based therapies are far from being safe and effective for the treatment of CRAB infections (Table 2).

Colistin-based combination therapies have been preferred over colistin monotherapy given colistin's suboptimal pharmacokinetics and pharmacodynamics. However, randomized controlled trials (RCTs) have not yet proven the superiority of combination therapy over colistin monotherapy. A recent international open-label RCT comparing colistin plus meropenem versus monotherapy with colistin against serious carbapenem-resistant Gram-negative infections did not show a statistical difference in mortality rates between two treatment arms (10). BSI and ventilator-associated pneu-

TABLE 2 Limitations of current therapeutic options

Issue	Colistin	Tigecycline	Minocycline	Amikacin	Sulbactam
Pharmacokinetic issues					
Narrow therapeutic spectrum	✓				
Low or inconsistent drug levels					
Plasma	✓	✓			
Lung	✓	✓			
Urine		✓			
Toxicity					
Nephrotoxicity	✓			✓	
Neurotoxicity	✓				
Resistance					
High resistance rates		✓	✓	✓	✓
Heteroresistance	✓				
Breakthrough	✓	✓			
Only in combination			✓	✓	✓
Increased mortality		✓			

monia (VAP) constituted 87% of the infections, and CRAB was the primary pathogen (77%). Three previous RCTs which compared colistin with colistin-rifampin or colistin-fosfomycin in CRAB infections, including BSI, did not find evidence for the superiority of combination therapy in mortality (11–13). It should be noted that more than 70% of those in the Durante-Mangoni et al. study receiving colistin without rifampin actually received other antibiotics (12). In the study by Aydemir et al. (11), the mortality rate was in fact lower in the colistin-rifampin arm (8/21 [38.1%]) than in the colistin arm (14/22 [63.6%]), but the difference did not reach statistical significance ($P = 0.171$). Until the results of a large well-designed double-blind randomized trial comparing the colistin-carbapenem combination versus colistin monotherapy (14) are available, it may still be considered that the question of combination therapy is not definitively answered.

Tigecycline, developed for the treatment of multidrug-resistant (MDR) pathogens and having potent *in vitro* activity against *A. baumannii*, has been in use for the treatment of CRAB infections since 2006 (15). Though only licensed for complicated intra-abdominal infections (cIAI), skin and soft tissue infections (cSSSI), and community-acquired bacterial pneumonia (CABP), it has been widely used for the treatment of various other infections caused by CRAB (16). Yet, tigecycline suffers from pharmacokinetic issues, such as low plasma levels, limiting its use in BSI. In addition, its use in VAP was hampered when a phase III RCT showed tigecycline to be inferior to the comparator drug and to have higher mortality rates for VAP patients (17). The results from several recent studies and a meta-analysis are in line with these discouraging results (18–20), and these combined with increasing rates of tigecycline resistance among CRAB disfavor its use.

Minocycline is an older tetracycline with considerable *in vitro* activity against CRAB. It is the only agent against CRAB which can be administered by the oral route. High susceptibility rates (72.1% in the United States and 81.4% in Thailand) were shown in some studies (21), although resistant strains are not infrequent (22, 23). Lashinsky et al. recently reviewed seven retrospective studies which evaluated the use of minocycline alone or in combination with other agents against MDR *A. baumannii* infections and found high clinical and microbiological success rates (78.2% and 50% to 89%, respectively) (21). However, one should be cautious while interpreting the results of this review, since there were only 126 patients, 94 of whom were treated with combination therapy, and most patients (74.6%) suffered from respiratory tract infections. A new intravenous formulation of minocycline was placed in the U.S. market in 2015, and a pharmacokinetic study (Acute Care Unit MINocycline [ACUMIN]) to determine optimal dosing for the critically ill is ongoing (24). Although high susceptibility rates in some series and good safety profile are encouraging, minocycline's role as an anti-CRAB agent needs further investigation.

Amikacin is another drug used as an anti-CRAB agent because it retains *in vitro* activity against some strains. However, its nephrotoxicity and high resistance rates (68% to 100%) limit its systemic use (3). A large RCT comparing inhaled amikacin as adjunctive therapy to the standard of care in VAP patients failed to demonstrate its superiority over the standard of care and a placebo (25).

Sulbactam is a β-lactamase inhibitor with intrinsic activity against *A. baumannii*. The efficacy of sulbactam-containing regimens has been explored in several studies, and it is suggested as an anti-CRAB drug (26); higher doses were found to be effective against CRAB in some small studies (27). However, as with amikacin, high resistance rates among CRAB may limit its potential (28).

Various combinations of these drugs have been used for the treatment of CRAB infections; yet, combination therapies were not found to be superior over monotherapies in preventing resistance and improving clinical outcomes, even though the combination therapies may be better at microbiologic eradication (29–32).

None of the recent combinations of β-lactams and β-lactamase inhibitors, i.e., ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, or imipenem-relebactam, have clinically useful activity against CRAB, and the activity of the new aminoglycoside plazomicin is limited to a minority of strains, which may partly be explained by the increasing frequency of ribosomal methyltransferases in *A. baumannii* (33).

NEW THERAPEUTIC OPTIONS

Siderophore cephalosporins. (i) Cefiderocol. Cefiderocol (S-649266) is a recently developed novel cephalosporin conjugated with a catechol siderophore on its side chain. Cefiderocol has a distinctive active uptake mechanism and stability against many β-lactamase classes, which provide enhanced penetration of bacterial cell and activity against highly resistant Gram-negative bacteria, including CRAB (34).

In *in vitro* studies, cefiderocol was shown to be potent against OXA-23, OXA-40, and OXA-58 as well as NDM- and IMP-producing *A. baumannii* isolates, with MIC_{90}s ranging from 1 to 8 μg/ml (35–40). However, it seems to be less active against some strains of *A. baumannii* that express OXA-23 and OXA-40 (38, 40, 41).

Characterization of the carbapenemases of CRAB strains from a global surveillance study with a large collection of CRAB isolates showed that the MIC_{90} was 1 μg/ml for OXA producers and GES producers and 4 μg/ml for NDM producers (41). Among 689 CRAB strains, there were 22 strains with MICs of >4 μg/ml (8, 16, 32, and 64 μg/ml). Twenty-one of these were OXA producers (15 OXA-23 strains and 6 OXA-40 strains), and one strain was a GES producer (Table 3). Another surveillance study, which tested the isolates collected 1 year later, showed that the MIC_{90} and the highest MIC for cefiderocol were 2 μg/ml and >256 μg/ml, respectively (42). Twenty-two of 558 strains had MICs of >4 μg/ml. The carbapenemase types of these strains have not yet been characterized. In two other studies, CRAB strains with cefiderocol MICs of ≥ 8 μg/ml similarly were OXA-23 (7 and 2 strains) and OXA-24 (0 and 1 strain) producers (38, 40). Although susceptibility breakpoints for cefiderocol have not yet been established, a recent study defined "resistant" as an MIC of ≥ 16 μg/ml and identified 6 resistant CRAB strains, two of which were OXA-23 producers (43). The cefiderocol MIC_{90} was 1 μg/ml in another collection of CRAB strains, and there were 28 strains out of 758 with MICs of >8 μg/ml (44). Interestingly, in a study from Greece, there were not any CRAB strains with MICs of >2 μg/ml (45).

For *in vivo* studies, the efficacy of humanized exposures of cefiderocol was evaluated in animal infection models. In immunocompetent rats infected with CRAB clinical isolates, a 2-g equivalent of cefiderocol infused every 8 h (3 h infusion) decreased the microbiologic load by >3 $\log_{10}$ after 4 days (46). In another study, immunocompromised mice were infected with CRAB, and a ≥ 1-$\log_{10}$ reduction in microbiologic load was observed 24 h after 2 g equivalent of cefiderocol was infused every 8 h (3 h infusion) (47). In the second study, the ≥ 1-$\log_{10}$ reduction was observed only in 2 of 28 strains (19 *A. baumannii* strains) with MICs of ≥ 8 μg/ml, whereas the growth of most

TABLE 3 Studies evaluating cefiderocol against CRAB[a]

Reference no.	β-Lactamase(s)	No. of CRAB isolates	No. of isolates with MIC >4 or 8 μg/ml[b]	MIC data (μg/ml)		
				MIC_{50}	MIC_{90}	Range
35	OXA	101	NA	0.25	1	≤0.03 to >64
36	NA	368	38	0.25	8	0.015 to >256
37	NA	173 (NoA)[c]	24	0.25	1	≤0.002 to 8
		595 (EU)		0.12	1	0.004 to 64
41	NDM	2	0	NA	4	NA
	OXA-23	543	15	0.12	1	≤0.02 to 16
	OXA-40	124	6	0.12	1	0.04 to 64
	OXA-58	13	0	0.12	1	0.06 to 1
	GES	7	1	NA	NA	0.25 to 8
42	NA	558	22	0.5	2	≤0.002 to >256
136	NA	44	0	0.12	1	0.015 to 4
44	NA	758	28	NA	1	≤0.004 to 64
39	OXA-23	1	NA	NA	0.063	NA
	OXA-58	1	NA	NA	1	NA
	OXA-26, OXA-51-like	1	NA	NA	0.5	NA
	OXA-51-like	1	NA	NA	0.5	NA
	OXA-23, OXA-51-like	1	NA	NA	≤0.031	NA
	OXA-48	1	NA	NA	≤0.031	NA
45	NA	107	0	0.06	0.5	0.03 to 2
38	OXA-23/-40/-58/-72	85	7	0.12	4	0.03 to 64
	NDM-1, IMP-4	2	NA	NA	NA	NA
137	OXA-23	5	0	NA	NA	0.03 to 0.5
40	Random strains	104	0	0.125	2	≤0.063 to 4
	All BL carriers	29	0	0.5	8	0.03 to >32
	IMP-1	2	0	NA	NA	0.12 to 0.25
	OXA-23	12	2	NA	NA	0.03 to >32
	OXA-24	8	1	NA	NA	0.12 to 8
	OXA-51/IS*Aba1*	2	0	NA	NA	0.5 to 1
	OXA-58	5	0	NA	NA	0.12 to 4

[a]NA, not available; BL, β-lactamase.
[b]MIC was >4 μg/ml for studies 35, 36, 37, and 41, >8 μg/ml for study 42, and ≥8 μg/ml for studies 38 and 40.
[c]NoA, North America; EU, Europe.

isolates with MICs of ≤4 μg/ml could be reduced by ≥1 $\log_{10}$, suggesting a susceptibility breakpoint for cefiderocol.

In clinical studies, cefiderocol was found to be superior to imipenem-cilastatin for the treatment of complicated urinary tract infections (cUTI) in a phase III RCT (48). The primary pathogens were *Escherichia coli* and *Klebsiella pneumoniae*, and there were not any CRAB strains among other pathogens. Two other phase III trials about cefiderocol are currently recruiting patients. One of them compares cefiderocol with "best available therapy" for severe infections (cUTI, BSI, HAP/VAP, and sepsis), and the other one compares the drug with meropenem for health care-associated pneumonia (HCAP), HAP, and VAP (49, 50). It is expected that both of these studies will enroll considerable numbers of patients with CRAB infection.

(ii) Other siderophores. GSK-3342830 is another siderophore cephalosporin with considerable activity against CRAB (51, 52). A collection of 94 *A. baumannii* clinical isolates (71.3% carbapenem nonsusceptible) had $MIC_{50/90}$ values of 0.06/0.5 μg/ml, and the MIC range was ≤0.03 to 4 μg/ml. However, phase I trials of GSK-3342830 have been terminated (53).

Fimsbactin, an *A. baumannii*-selective siderophore, was coupled to daptomycin by Ghosh et al., with the hypothesis that coupling of a Gram-negative-targeted siderophore to daptomycin could help transfer daptomycin directly into the cytoplasm, bypassing the need for outer membrane penetration. The resulting conjugate had potent *in vivo* and *in vitro* activity against 10 reference *A. baumannii* strains, including MDR strains (54). For *in vivo* studies, mice infected with *A. baumannii* ATCC 17961 were treated with ciprofloxacin, daptomycin, or fimsbactin conjugate. Saline treatment was used as a control. All mice in the treatment groups other than fimsbactin conjugate were dead after day 1, whereas 4 out of 5 mice treated with fimsbactin conjugate

TABLE 4 Studies evaluating eravacycline against CRAB

Reference no.	β-Lactamase(s)	No. of CRAB isolates	No. of isolates with MIC >4 μg/ml	MIC data (μg/ml)		
				MIC_{50}	MIC_{90}	Range
56		163		0.5	1	0.12–8
59		55		0.5	1	0.031–2
28	OXA-23	231		0.5	1	
	OXA-40	17		0.25	1	
	OXA-58	27		0.5	0.5	
	OXA-51[a]	9				0.125–0.5
	Overall	286[b]	1	0.5	1	≤0.06–8
57	NDM	5	0			0.13–0.25
	OXA-23/-40/-51/-58	39	0	0.5	1	≤0.06–2
	Tig[r] plus OXA-23[c]	5	2	4	8	1.0–8.0
	Overall	59[d]	2	0.5	1	≤0.06–8
58	OXA-23	58			1	
	OXA-24	2				
	KPC	1				
	adeB expression	38[e]		0.5	2	0.06–4
	Overall	158[f]		0.5	1	≤0.015–8
61	NDM	62				
	OXA-48	27				
	VIM	15				
	Overall	104		0.5	4	
138	OXA	8				
	NDM	4				
	Total	14		0.25	1	0.031–2
139		193		1	2	0.12–8
62	NDM, OXA-48, VIM	16		0.125	8	
60		707		1	2	0.06–8
140		52		0.5	2	≤0.016–4

[a]Hyperproduced.
[b]One isolate with OXA-23 and OXA-58, 1 isolate with NDM-1.
[c]Tig[r], tigecycline resistant.
[d]Forty-nine CRAB isolates and 10 carbapenem-susceptible *A. baumannii* isolates.
[e]Twenty-six CRAB isolates and 12 carbapenem-susceptible *A. baumannii* isolates.
[f]One hundred nine CRAB isolates and 49 carbapenem-susceptible *A. baumannii* isolates.

survived (54). Further development of fimsbactin-daptomycin is unknown at this stage. It is worth considering the inactivation of daptomycin in the lungs, which may diminish the potential utility of this investigational agent for CRAB respiratory tract infections.

GT-1, siderophore cephalosporin developed by Geom Therapeutics, is claimed to have activity against CRAB both *in vitro* and *in vivo* in mice. According to the information obtained from the drug developer company's website, it will enter phase I clinical studies in 2018 under a contract with the National Institute of Allergy and Infectious Diseases (55).

Tetracyclines. (i) Eravacycline. In *in vitro* studies, eravacycline (TP-434), a novel fluorocycline of the tetracycline family, shows activity against a broad range of pathogens, including MDR and XDR Gram-negative, Gram-positive, and anaerobic pathogens. Eravacycline MICs were found to be 2- to 8-fold lower than tigecycline MICs against CRAB (28, 56–58) (Table 4). The drug is also active against colistin-resistant and ceftazidime-avibactam-resistant strains (28, 59). The eravacycline $MIC_{50/90}$ values for CRAB were 1 and 2 μg/ml in a large collection of CRAB isolates (60). Similar values were shown ($MIC_{50/90}$, 0.5/1 μg/ml) in several other studies where isolates produced OXA-23, OXA-40, or OXA-58 or had overexpression of OXA-51 (28, 57, 58). The production of OXA carbapenemases did not change the eravacycline MICs for CRAB, whereas NDM-, OXA-48-, or VIM-producing strains had MIC_{90}s of 4 to 8 μg/ml (61, 62). Increased eravacycline MIC values were also associated with increased expression of the efflux pump AdeABC. Eravacycline MIC and the expression of *adeB* showed a significant correlation among 38 *A. baumannii* isolates (26 CRAB isolates) which did not carry any of the OXA genes (MIC range, 0.06 to 4 μg/ml) (58). Eravacycline maintained potency against isolates carrying tetracycline efflux pump genes (59).

TABLE 5 Studies evaluating TP6076 against CRAB

Reference no.	β-Lactamase(s)	No. of CRAB isolates	No. of isolates with MIC >4 μg/ml	MIC data (μg/ml)		
				MIC_{50}	MIC_{90}	Range
68		121		0.03	0.06	≤0.002–0.12
67	Overall	326	0[a]	0.06	0.125	0.008–0.5
	OXA-23	255				
	OXA-40	23				
	0XA-58	36				
	OXA-51[b]	10				
	NDM	1				
141		41	0	0.008	0.063	002–0.25

[a]All isolates had MICs of <0.5 μg/ml.
[b]Overexpressed.

The efficacy of eravacycline was shown in several animal studies (63) and in a phase III clinical trial in the setting of cIAI. The drug was noninferior to ertapenem in patients with cIAI, but septic patients and patients with high acute physiology and chronic health evaluation (APACHE) II scores were excluded (64). There were only 3 and 4 CRAB isolates among 220 and 226 isolates in the eravacycline and ertapenem arms, respectively. In a successive RCT, the drug was found to be noninferior to meropenem for the treatment of cIAI (65). Five hundred patients were randomized (39.8% complicated appendicitis and 60.2% other diagnoses, including complicated cholecystitis, intestinal perforation, and stomach/duodenal perforation), and there were 12 *Acinetobacter* spp. among 400 isolates. The U.S. FDA has approved eravacycline for the treatment of cIAI in adults age 18 years and older. However, eravacycline failed an initial phase III cUTI trial and was found to be inferior to levofloxacin and subsequently in a second phase III cUTI study versus ertapenem (66).

(ii) TP-6076. TP-6076 is another fluorocycline antibiotic being developed for the treatment of MDR pathogens. TP-6076 MICs were very low (MIC range, 0.008 to 0.5 μg/ml) against clinical CRAB isolates producing OXA carbapenemases, including 44 colistin-resistant strains (67) (Table 5). Eravacycline and tigecycline $MIC_{50/90}$ values were 0.5/1 and 1/2 μg/ml, respectively, for the same isolates (67). The TP-6076 $MIC_{50/90}$ values were 0.03/0.06 μg/ml when tested against 121 clinical isolates from Greek hospitals between 2015 and 2017 (68). TP-6076 activity was minimally affected by recombinant overexpression of several tetracycline efflux pumps, and it was also potent against clinical CRAB isolates expressing *tetA* (3 isolates) and *tetB* (18 isolates) efflux pump genes, showing a maximum MIC_{90} of 1 μg/ml (69). However, TP-6076 is a substrate of the AdeABC efflux pump (69). TP-6076 was shown to be bactericidal in a mouse CRAB pneumonia model, where a ≥3-log_{10} reduction in mean lung CFU was observed at 24 h (69). The drug is currently being evaluated in phase I trials (70).

New non-β-lactam–β-lactamase inhibitors paired with existing β-lactam antibiotics. (i) ETX2514. ETX2514 is a broad-spectrum diazabicyclooctanone (DBO) β-lactamase inhibitor similar to avibactam and relebactam. ETX2514 inhibits penicillin-binding protein 2 (PBP2) and enhances β-lactam activity (71). It has been developed by modifying the DBO scaffold to cover a broad range of OXA β-lactamases (72). EXT2514 is being developed in combination with sulbactam. Sulbactam-ETX2514 is a potent combination against CRAB, whereas combinations with imipenem and meropenem did not decrease the MICs to susceptible levels (72). Sulbactam-ETX2514 was found to be active against a large collection of CRAB strains (91% OXA carriers) ($MIC_{50/90}$, 1/4 μg/ml) and remained active against 56 colistin-resistant strains with an MIC of 2 μg/ml (73). Similar MICs of sulbactam-ETX2514 were observed among 84 CRAB isolates, 54% of which encoded class A in addition to class C and D β-lactamases (60 strains encoded OXA-23, OXA-40, and OXA-58) (72). It should be noted that the number of isolates with MICs of >4 μg/ml were 4 among 731 isolates in those studies (Table 6). The frequency of spontaneous resistance to sulbactam-ETX2514 is low (74).

In vivo studies of sulbactam-ETX2514 showed a dose-dependent reduction in MDR *A. baumannii* bacterial counts, and >1-log (72) or >2-log (75) drops in CFU counts were

TABLE 6 Studies evaluating ETX2514 (4 μg/ml) against CRAB

Reference no.	β-Lactamase(s)	No. of CRAB isolates	No. of isolates with MIC >4 μg/ml	BL drug in combination	MIC data (μg/ml)		
					MIC_{50}	MIC_{90}	Range
72	Various[a]	195		IPM	0.5	16	≤0.06 to >64
				MEM	1	16	≤0.06 to >64
				CAZ	8	32	≤0.06 to >64
				SUL	1	4	≤0.06 to 32
				ATM	32	>64	≤0.06 to >64
		84		SUL	2	4	0.25 to 16
73	Overall	731	4	SUL	1	4	≤0.06 to 32
	OXA	668	3		1	4	≤0.06 to 32
	MBL	1	1			32	
	GES	6	0				0.5 to 4
	ESBL[b]	5	0				1.0 to 2.0
	bla negative	51	0		2	4	0.25 to 4
142	OXA-23, OXA-58	72[c]		SUL	1	2	

[a]Of the strains, 52% encoded class A in addition to class C and D β-lactamases, and 60 strains harbored either OXA-23, OXA-40, or OXA-58.
[b]ESBL, extended-spectrum β-lactamase.
[c]The total number of *A. baumannii* isolates was 72, and more than half of the isolates were MDR.

achieved when sulbactam concentrations exceeded the combination MIC of 0.5 μg/ml for 50% of the dosing interval. The strain used in these murine infection models did not harbor any OXAs other than OXA-72 and OXA-66 (72). A phase I study investigating ETX2514 in combination with either sulbactam or imipenem-cilastatin is completed, and the combinations have been found to be generally safe among healthy volunteers (76, 77). Another phase I study conducted to determine plasma and intrapulmonary concentrations of ETX2514 and sulbactam in healthy subjects is completed, but the results are not published yet (78). A further phase I study to evaluate ETX2514-sulbactam in patients with renal impairment and a phase II study to evaluate the drug in hospitalized patients with cUTI are ongoing (79, 80).

(ii) WCK 4234. WCK 4234 is another DBO β-lactamase inhibitor being developed in combination with meropenem as WCK-5999. WCK 4234 is active against several carbapenemases from classes A, C, and D, including OXA-23 and OXA-51 (71, 81, 82).

The WCK 4234 $MIC_{50/90}$ values were 2/8 μg/ml when combined with meropenem at a dose of 8 μg/ml against a large collection of *A. baumannii* isolates (83, 84). In this study, 62.8% of the isolates were carbapenem nonsusceptible, but carbapenem resistance genes were not identified. In another study, the $MIC_{50/90}$ values of the meropenem-WCK 4234 combination were 2/4 μg/ml against OXA-23-producing CRAB strains (82). The same combination was less effective against OXA-40-producing strains ($MIC_{50/90}$, 4/8 μg/ml). Similarly, both meropenem and imipenem MICs were reduced to 2 μg/ml or below by WCK 4234 in 9 of 10 OXA-23-producing CRAB isolates, whereas OXA-40-producing isolates stayed resistant (81). WCK 4234 reduced imipenem but not meropenem MICs for isolates producing OXA-58 (Table 7). OXA-51 hyperproducers were also suppressed with WCK 4234-potentiated carbapenems, whereas metallo-β-lactamase (MBL) producers remained resistant (81).

In summary, WCK 4234 in combination with either meropenem or imipenem is effective against OXA-23 producers and OXA-51 hyperproducers. OXA-58 can be inhibited by only imipenem-WCK 4234 combinations, whereas OXA-40 and MBL producers remain resistant to imipenem or meropenem potentiated with WCK 4234. The WCK 4234-meropenem combination showed efficacy against MDR *A. baumannii* strains producing OXA-23 and OXA-51 in murine peritonitis and neutropenic lung infection models (71). No clinical studies have yet been commenced.

(iii) LN-1-255. LN-1-255 is a non-β-lactam–β-lactamase inhibitor from the penicillanic acid sulfone family. It is active against class D β-lactamases *in vitro* (85, 86). The inhibition efficiency of LN-1-255 was shown to be superior to those of tazobactam and avibactam in kinetic assays (85). LN-1-255-carbapenem combinations were tested against isogenic CRAB strains and clinical isolates producing various OXA carbapenemases, i.e., OXA-23, OXA-40, OXA-58, and OXA-143 (85). LN-1-255 showed synergy

TABLE 7 Studies evaluating WCK 4234 against CRAB

Reference no.	β-Lactamase(s)	No. of CRAB isolates	No. of isolates with MIC >4 μg/ml	BL drug in combination	MIC data (μg/ml)		
					MIC_{50}	MIC_{90}	Range
81	OXA-23	10	0	IPM			0.25–4
			0				0.5–4
			1	MEM			0.5–8
			0				0.5–4
	OXA-40		5	IPM			1.0–32.0
			4				0.5–16
			6	MEM			1.0–32.0
			4				0.5–16
	OXA-51-IS*Aba1*		0	IPM			0.5–4
			0				0.25–2
			0	MEM			0.25–4
			0				0.5–4
	OXA-58		0	IPM			1.0–4.0
			0				0.5–4
			1	MEM			0.5–16
			1				0.5–16
	NDM	5	5	IPM			≥128
			5				≥128
			5	MEM			≥128
			5				≥128
			5	IPM			≥128
			5				≥128
			5	MEM			≥128
			5				≥128
82	OXA-23	32	3	MEM	2	4	
			1		2	4	
	OXA-24	17	16	MEM	8	16	
			14		4	8	
	Overall	55[a]	4	MEM	4	8	
83, 84		639[b]		MEM	2	8	

[a]One strain carried both OXA-23 and OXA-24, and 1 strain carried OXA-23, OXA-24, and OXA-58.
[b]Of the isolates, 62.8% were CRAB.

with carbapenems and decreased their MICs by 2- to 32-fold, to ≤ 2 μg/ml in transformant *A. baumannii* strains. Similar results were obtained with the clinical isolates, although the MICs were slightly higher than those observed in the transformants, mainly in the clinical isolate carrying OXA-40 (85).

Although OXA-48 does not carry the hydrophobic bridge important for the inhibition by LN-1-255, it was inhibited by LN-1-255-carbapenem combinations in both isogenic strains and clinical isolates of *Enterobacteriaceae* (86).

(iv) VNRX-5113. VNRX-5113 is a β-lactamase inhibitor which is claimed to inhibit MBL activity in MDR Gram-negative bacilli, including *A. baumannii*. The partner β-lactam is currently unspecified. A phase I study, funded by the NIH, was initiated in 2017. The information about the drug is obtained mainly from the drug developer's website, and there is not yet further information in the public domain (87).

(v) WCK 5153 and zidebactam. Zidebactam (WCK 5107) and WCK 5153 are DBOs that also inhibit PBP2 and show a potent β-lactam enhancer effect against Gram-negative pathogens, including *A. baumannii* (71, 88). They are also active against MBL-producing *K. pneumoniae* strains *in vitro* (89). WCK 5153 and zidebactam decreased the sulbactam MIC from 16 to 2 μg/ml for MDR *A. baumannii* (OXA-23-producing ST2 international clone) (88). Combinations with cefepime were not as effective, although the cefepime MIC was lowered from 64 to 16 μg/ml, suggesting some enhancer effect (88). Zidebactam, in combination with cefepime (WCK 5222), is being developed as MDR/XDR therapy mainly against *Pseudomonas aeruginosa* rather than CRAB. Yet, cefepime-zidebactam was found to be efficacious in murine peritonitis and neutropenic lung infection models against MDR *A. baumannii* strains that express OXA-23 and OXA-51, among others (71). The drug completed two phase I clinical trials

(90, 91), and another phase I trial to investigate the pharmacokinetics of the drug in patients with renal impairment is currently recruiting participants (92).

New β-lactam antibiotics. (i) AIC-499. AIC-499 is a new β-lactam antibiotic being developed in combination with a β-lactamase inhibitor (currently unspecified). It is claimed to have activity against MDR *A. baumannii* and MDR *P. aeruginosa* strains. It is in phase I trials, but information is not currently registered on a government trial registry. According to the information obtained from the drug developer company's website, a phase I study is conducted in 48 healthy volunteers in a single center at the Medical University of Vienna, Austria. This single-dose study is planned to be followed by a multiple-ascending-dose part in 36 volunteers. Clinical trials are being supported by the Innovative Medicines Initiative (IMI) within the COMBACTE-MAGNET project (93).

(ii) FSI-1671. FSI-1671 is a new class of carbapenems which possesses activity against *A. baumannii*. The FSI-1671-sulbactam combination was active ($MIC_{50/90}$, 0.25/1 μg/ml; MIC range, ≤0.008 to 4 μg/ml) against 85 clinical *A. baumannii* isolates, including OXA producers, though the number of CRAB isolates is not specified (94). The combination also showed *in vivo* efficacy against CRAB-infected mice (95). Further development of FSI-1671 is unknown at this stage.

Polymyxin B-derived molecules. (i) SPR741. SPR741 (formerly NAB74) is a polymyxin B (PMB)-derived antibiotic adjuvant that permeabilizes the Gram-negative membrane. It does not exhibit Gram-negative activity itself and is specifically designed to minimize nephrotoxicity. Potentiation of rifampin activity with SPR741 against *A. baumannii*, including clinical isolates, has been shown in several *in vitro* studies using checkerboard or time-kill analyses (96–98). SPR741 at 8 μg/ml was able to potentiate the activities of rifampin and meropenem, reducing the MICs from 128 to 0.5 μg/ml and from 4 to 0.016 μg/ml, respectively, against 17 CRAB strains (clinical isolates and reference strains) (97). Similarly, the rifampin MIC was at least 4-fold reduced in the presence of SPR741 against 28 reference strains (57% nonsusceptible to carbapenem) (96). A SPR741-rifampin combination achieved significant lung concentrations and 2-log_{10} reduction in bacterial burden in murine lung infection models (96, 99). SPR741 was found to be generally well tolerated in phase I clinical trials (100, 101).

(ii) FADDI-287. FADDI-287 is a novel polymyxin analogue with an improved safety profile. It has greater potency than PMB against CRAB (102). The $MIC_{50/90}$ values of FADDI-287 were 0.25/0.5 μg/ml against 210 CRAB isolates (MIC range, 0.25 to 64 μg/ml), whereas the PMB $MIC_{50/90}$ values were 1/2 μg/ml (MIC range, 0.25 to 64 μg/ml) (102). FADDI-287 and PMB inhibited 91.4% and 11.4% of the isolates at an MIC of ≤0.5 μg/ml, respectively. FADDI-287 showed promising efficacy and reduced renal toxicity in mouse thigh and rat lung infection models against *A. baumannii* (103).

The aminoglycoside apramycin. Apramycin is an aminoglycoside antibiotic used in veterinary medicine. Its resistance to inactivation by most aminoglycoside-modifying enzymes makes it an attractive therapeutic option against MDR Gram-negative microorganisms. The $MIC_{50/90}$ values of apramycin were found to be 16/64 μg/ml against carbapenem and aminoglycoside-resistant 594 *A. baumannii* isolates from Greek hospitals (MIC range, 2 to 256 μg/ml), and 88.6% of the strains were inhibited at a concentration of ≤32 μg/ml, which is the apramycin breakpoint of susceptibility as per the National Antimicrobial Resistance Monitoring System (104). In a previous study, similar values were observed ($MIC_{50/90}$, 8/32 μg/ml; MIC range, 2 to 256 μg/ml) against 104 *A. baumannii* isolates (89% CRAB isolates) (105). Apramycin efficacy was also tested in a murine thigh infection model (106). Neutropenic mice were inoculated with three strains of *A. baumannii* that had apramycin MICs of 2, 16, and 64 μg/ml and were treated with apramycin 2 h postinfection. There was at least a 4-log_{10} reduction in CFU in all three strains at 24 h postinfection (106). There are no clinical studies as of date.

Other drug candidates. Molecules that play a role in lipid A biosynthesis have been attractive targets for antibiotic development. The most promising among them is LpxC, a zinc-dependent deacetylase. Inhibition of LpxC increases the antibiotic susceptibility of *A. baumannii* (107), including XDR clinical isolates (108). The $MIC_{50/90}$ values of a new

LpxC inhibitor were 0.8/3.2 μg/ml (MIC range, 0.5 to $\geq$64 μg/ml) when tested on 25 clinical *A. baumannii* isolates, including 19 MDR/XDR strains (7 OXA-23 producers and 1 OXA-40 producer) (109). An LpxC inhibitor, ACHN-975, failed human trials due to inflammation at the infusion site. Nevertheless, this new class of antibiotics may be promising agents for the treatment of CRAB infections if safety and pharmacokinetic properties are optimized and their activity and efficacy against CRAB infections are supported by further studies (110).

Another drug candidate with *in vitro* activity against CRAB is RX-P873. It binds to a conserved region in the ribosome and inhibits protein synthesis. The $MIC_{50/90}$ values of RX-P873 were 0.5/1 μg/ml (MIC range, 0.12 to 4 μg/ml) against 202 clinical *A. baumannii* isolates (52.5% carbapenem resistant) (111). No further studies have been reported on this molecule since 2015, and the latest information from the drug developer company's website is from 2014.

Other therapeutic options. (i) Phage therapy. In the era of MDR microorganisms with strictly limited therapeutic options, bacteriophage therapy attracts many clinicians in spite of numerous unanswered questions about its use. Phages were discovered a century ago (112), although the first phages specific to MDR *A. baumannii* and CRAB were only characterized in 2010 and 2012 (113, 114). CRAB infections have been treated with phages successfully in animals (115–121). Data from human infections remain scarce.

Schooley et al. treated a septic patient with phages (122). This was a 68-year-old diabetic man who developed gallstone pancreatitis and a pancreatic pseudocyst, from which PDR *A. baumannii* strains resistant to meropenem, amikacin, trimethoprim-sulfamethoxazole, tetracycline, ciprofloxacin, and colistin were isolated. Even though the patient was treated with combination therapies according to synergy testing results, MDR *A. baumannii* strain was repeatedly isolated from multiple sites. The patient eventually deteriorated and required vasopressors. At this time, the phage cocktail was administered, initially into the pseudocyst cavity and intra-abdominally and later intravenously. The patient improved with this therapy and ultimately had a favorable clinical outcome. Another patient infected with PDR *A. baumannii* was treated with bacteriophages by the same group (123). This was a 77-year-old man who underwent a craniectomy due to assault resulting in subdural and epidural empyema. PDR *A. baumannii* was isolated from intraoperative cultures. The patient did not improve with combination antibiotic therapies and was put on phage therapy. Phages were administered intravenously for 19 days. Although the craniotomy site and the skin flap healed well, the patient died on day 20. Phage therapy could not be administered intrathecally for this patient, which may be one of the reasons for the failure of phage therapy, another being the severity of his underlying condition.

In another study from Russia, one of the few countries where phage therapy is widely used (124), Bochkareva et al. presented data on 42 intensive care unit (ICU) patients treated with phages. Of those patients, 87.5% had MDR *A. baumannii*, *K. pneumoniae*, and *P. aeruginosa* growth in their endotracheal aspirate, blood, urine, and feces. They had received repeated doses of a phage cocktail either therapeutically or prophylactically. The phage cocktail was defined as "therapeutic and prophylactic product (TPP)" and included two phage strains per each bacterium (*A. baumannii*, *K. pneumoniae*, *P. aeruginosa*, and *Staphylococcus aureus*). The efficacy of TTP was determined 24 h after the final dose of treatment, and anti-phage immunity was detected after 2 to 3 weeks. It was shown that 54 to 62.5% of patients had "sanitation of the infected loci." The authors stated that repeated doses of phages do not eradicate infection more efficiently than the single dose and suggest that repeated doses have undesired consequences, such as the development of anti-phage antibodies. A change in the composition of the phage strains is required for future treatments (125). In another study from Russia, 14 patients with MDR *A. baumannii*, *K. pneumoniae*, *P. aeruginosa*, and *S. aureus* growth in several samples, including endotracheal aspirate, blood, and urine, had a microbiologic response to a 3-day phage therapy (126).

These results, though promising, display the hurdles of the bacteriophage treatment process. Phages are very host specific, and preparation of the phage cocktail in advance is difficult (127). The dosing route and schedule of phages are not known for different body site infections. Schooley et al. administered phages through intracystic, intraabdominal, and intravenous routes, whereas Russian researchers used gastrointestinal (oral and intragastric) and endotracheal routes. There are not clearly defined dosing intervals currently, and unfavorable outcomes of multiple dosing may occur (125). It is necessary to detect anti-phage antibodies for a customized therapy with repeated doses. Another handicap of this therapeutic option is resistance as shown by Schooley et al, where one of the strains developed resistance to the bacteriophage cocktail 8 days after the initiation of therapy (122). This may in part be overcome with the development of new phages against the new resistant strain, which requires an active "on-demand" service for the rapid selection of new phage strains (125).

An RCT comparing phage therapy with antibiotics for cUTI in patients undergoing prostate resection is recruiting patients (128, 129). Finally, phages may have other promising uses in the fight against drug-resistant bacteria. Ho et al. used anti-CRAB phage aerosols to decontaminate patient rooms and showed that phage aerosols reduce CRAB infection rates (130).

(ii) Monoclonal antibodies. Development of monoclonal antibodies (MAbs) for the treatment of bacterial infections is challenging due to several host- and product-specific issues. Currently, there are three FDA-approved antibacterial MAb products (against *Bacillus anthracis* and *Clostridium difficile*) and at least nine MAbs (mainly against *S. aureus* and *P. aeruginosa*) that are in clinical trials (131). Monoclonal *A. baumannii* antibodies have been used for protection from sepsis and pneumonia and treatment of wound infections in animal models (132, 133). Nielsen et al. recently developed an MAb active against XDR *A. baumannii*. The new MAb, called C8, showed antibacterial activity alone and in combination with colistin against XDR *A. baumannii in vitro* and in mice, and it retained activity after humanization (134). AR-401 is another fully human MAb claimed to be developed against *A. baumannii* (135).

CONCLUSION

CRAB is arguably the most troublesome Gram-negative microorganism due to its great capacity for resistance development. New agents recently approved for drug-resistant Gram-negative bacilli are effective against KPC producers or carbapenem-resistant *P. aeruginosa* but not against CRAB.

Cefiderocol is likely to be the first of the new agents active against CRAB to be approved for clinical use. Its *in vitro* effectiveness against large collections of CRAB strains with a variety of resistance mechanisms provides much hope, as does its superiority over imipenem-cilastatin for the treatment of cUTI. However, there were very few *A. baumannii* strains in this clinical trial, so its real test will be in phase III trials for patients with serious infections, such as BSI and VAP. Cefiderocol-nonsusceptible strains of CRAB already exist before its approval, and a key question will be the effects of selection pressure once cefiderocol is used clinically.

Eravacycline, recently placed on the market, has better *in vitro* activity against CRAB than tigecycline. However, existing issues about tigecycline and the failure of eravacycline in phase III trials of cUTI diminish the expectations from this drug. Unfortunately, no trials to evaluate eravacycline efficacy on BSI and VAP are on the horizon.

Among other drug candidates, ETX2514 combined with sulbactam is in phase II studies. TP-6076, VNRX-5113, AIC-499, and SPR741 have commenced or completed phase I studies, though the available information in the public domain is limited for all of these compounds. Other new β-lactamase inhibitors (i.e., WCK 4234, LN-1-255, WCK 5153, and zidebactam) and apramycin are not yet in clinical studies, but their activity against CRAB isolates and efficacy in animal infections are promising. For future clinical trials to be informative and useful, they should include patients with severe infections from areas with high resistance rates. Such patients are the ones for whom the new drugs are needed the most.

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