



# Evidence for Efficacy of Cefiderocol against OXA-48-Containing Isolates from the APEKS-NP and CREDIBLE-CR Trials

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We were very interested to read the minireview by Boyd et al. (1) on the classification, identification, epidemiology, and treatment of OXA-48-like carbapenemase-producing *Enterobacteriales*. In their discussion of cefiderocol, the authors were correct to point out “it is unclear how many patients had OXA-48-like producers” with regard to the CREDIBLE-CR study (2). Aside from a single poster describing the outcomes of specific carbapenemases from the CREDIBLE-CR study (3), we have not published data specific to clinical efficacy in OXA-48-producing infections except for two cases of bacteremia (4). The authors also point out that registrational clinical trials that usually exclude patients with known carbapenem-resistant infections due to the inactivity of the control antibiotics provide limited high-quality information pertaining to molecularly characterized clinical data on OXA-48- and OXA-48-like pathogens.

Shionogi reviewed both the CREDIBLE-CR and APEKS-NP (5) clinical trial databases, where all pathogens were molecularly characterized. A total of 10 patients with OXA-48-positive *Enterobacteriales* who received cefiderocol were identified (Table 1). Seven were from CREDIBLE-CR, and three were from APEKS-NP. All characterized pathogens were *Klebsiella pneumoniae* species. Of note, three contained OXA-48 along with NDM-1 carbapenemase, and all contained other extended-spectrum (ESBL) and original-spectrum (OSBL) type beta-lactamases. All but two isolates had high-level resistance to meropenem (MIC > 8 μg/mL). All patients but one received cefiderocol as monotherapy, 7 of 10 (70%) patients were judged to have clinical cure at the test-of-cure assessment (cefiderocol MIC range, 0.12 to 4 mg/L), and all survived through day 28.

Although these numbers are small, the clinical and microbiological outcomes were consistent with the studies' overall findings of efficacy against *Enterobacteriales*. Together with the demonstrated *in vitro* stability of cefiderocol to OXA-48 hydrolysis (6) and the *in vitro* activity against OXA-48 producers (7–9), we are confident of the potential benefit of cefiderocol treatment for OXA-48-producing *Enterobacteriales*.

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The authors declare a conflict of interest. All authors are employees of Shionogi, the marketing authorisation holder for cefiderocol.

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**TABLE 1** Summary of CREDIBLE-CR and APEKS-NP database results for *Klebsiella pneumoniae*

Clinical study	Cefiderocol MIC ( $\mu\text{g/mL}$ )	Meropenem MIC ( $\mu\text{g/mL}$ )	Site of infection <sup>a</sup>	Country	Clinical outcome at TOC	Beta-lactamase profile <sup>b</sup>
CREDIBLE-CR	2	4	BSI/sepsis	Spain	Clinical failure	CTX-M-15; SHV-OSBL; TEM-OSBL; <b>OXA-48</b>
	4	>64	cUTI	Turkey	Clinical cure	CTX-M-15; SHV-OSBL; TEM-OSBL; <b>OXA-48</b> ; <b>NDM-1</b>
	0.12	32	cUTI	Turkey	Clinical cure	CTX-M-9-group; SHV-OSBL; TEM-OSBL; <b>OXA-48</b>
	1	16	cUTI	Turkey	Clinical cure	CTX-M-15; SHV-OSBL; TEM-OSBL; <b>OXA-232</b>
	1	8	cUTI	Turkey	Clinical cure	CTX-M-15; SHV-OSBL; TEM-OSBL; <b>OXA-48</b>
	4	>64	cUTI	Korea	Indeterminate	CTX-M-55; SHV-OSBL; <b>OXA-232</b> ; <b>NDM-1</b>
	1	>64	BSI/sepsis	Thailand	Clinical cure	CTX-M-15; SHV-OSBL; TEM-OSBL; <b>OXA-232</b> ; <b>NDM-1</b>
APEKS-NP	2	64	RTI	Ukraine	Clinical cure	CTX-M-1-TYPE; SHV-OSBL; TEM-OSBL; <b>OXA-48</b>
	1	64	RTI	Russia	Clinical cure	CTX-M-15; SHV-OSBL; <b>OXA-48</b>
	0.5	32	RTI	Georgia	Indeterminate	CTX-M-15; SHV-OSBL; TEM-OSBL; <b>OXA-48</b>

<sup>a</sup>BSI, bloodstream infection; cUTI, complicated urinary tract infection; RTI, respiratory tract infection.

<sup>b</sup>Beta-lactamases in bold type are carbapenemases.

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