Cefiderocol: An Overview of Its \textit{in-vitro} and \textit{in-vivo} Activity and Underlying Resistant Mechanisms

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Treatment of multidrug-resistant (MDR) Gram-negative bacteria (GNB) infections has led to a global public health challenge due to the bacterial resistance and limited choices of antibiotics. Cefiderocol (CFDC), a novel siderophore cephalosporin possessed unique drug delivery systems and stability to β-lactamases, has the potential to become first-line therapy for most aggressive MDR Gram-negative pathogens infection. However, there have been reports of drug resistance in the course of using CFDC. This study provides an overview of the \textit{in-vitro} and \textit{in-vivo} activity of CFDC and potential resistance mechanism was also summarized. In general, CFDC shows excellent activity against a broad range of MDR GNB pathogens including \textit{Enterobacteriaceae}, \textit{Klebsiella pneumoniae}, \textit{Pseudomonas aeruginosa}, \textit{Acinetobacter baumannii}, and \textit{Stenotrophomonas maltophilia}. The expressions of metallo-β-lactamases such as inosine 5’-monophosphate (IMP), Verona integron-mediated metallo-β-lactamase (VIM), and New Delhi metallo-β-lactamase (NDM) are associated with a higher resistance rate of CFDC. Carbapenem-resistant phenotype has little effect on the resistance rate, although the acquisition of a particular carbapenemase may affect the susceptibility of the pathogens to CFDC. For potential resistance mechanism, mutations in β-lactamases and TonB-dependent receptors, which assist CFDC entering bacteria, would increase a minimum inhibitory concentration (MIC)\textsubscript{90} value of CFDC against MDR pathogens. Since the development of CFDC, resistance during its utilization has been reported thus, prudent clinical applications are still necessary to preserve the activity of CFDC.

Keywords: Gram-negative bacteria, activity, cefiderocol, resistance mechanisms, cephalosporins (therapeutic use)

INTRODUCTION

As an ongoing challenge to global health, the emergence of antibiotic-resistant infections results in substantial morbidity and mortality (1). Gram-negative bacteria (GNB) are increasingly associated with high rates of antimicrobial resistance, especially for the carbapenem-resistant \textit{Enterobacteriaceae} (CRE), multidrug-resistant (MDR) \textit{Acinetobacter baumannii} (\textit{A. baumannii}), \textit{Klebsiella pneumoniae} (\textit{K. pneumoniae}), and \textit{Pseudomonas aeruginosa} (\textit{P. aeruginosa}) (2). Due to the current limited options of MDR pathogen-caused infections and the resistance for “cunning bacterias” to drugs, new therapeutic options are of particular concern and urgently necessary (3–5).
As a novel injectable siderophore cephalosporin, cefiderocol (CFDC) has been approved by the United States Food and Drug Administration (FDA) for the treatment of complicated urinary tract infections (cUTIs) in 2019, hospital-acquired bacterial pneumonia (HABP), and ventilator-associated bacterial pneumonia (VABP) caused by GNB in 2020. In a study consisting of 377 patients with GNB-induced cUTI, 73% of 252 patients in the CFDC group was cured according to clinical response and microbiological response compared with the imipenem-clastatin group (55% of 119 patients), indicating the good activity of CFDC (6). Same as other cephalosporins, the principal mechanism of CFDC is the inhibition of the cell wall by combining with penicillin-binding protein-3 (PBP-3), which the affinities [50% inhibitory concentrations (IC50s)] of cefiderocol for PBP-3 of Escherichia coli (E. coli) NIHJ JC-2, K. pneumoniae SR22291, P. aeruginosa ATCC 27853, and A. baumannii ATCC 17978 were 0.04 to 0.67 μg/ml (7). However, CFDC is more stable to β-lactamases because of its “Trojan horse” strategy (7). CFDC combines a cephalosporin core and a catechol-type siderophore, which are highly effective to acquire bacterial iron (Fe^{3+}). Through binding to bacterial iron transporter outer membrane protein, CFDC can enter the bacterial periplasmic space to avoid the degradation of β-lactamase produced by the pathogen (7, 8) (Figure 1). Therefore, it shows activity against GNB pathogens including extended-spectrum β-lactamases (ESBL)-producing GNB, CRE, P. aeruginosa, A. baumannii, K. pneumoniae, Klebsiella oxytoca, and Stenotrophomonas maltophilia (S. maltophilia) (9–19). Serratia marcescens, Citrobacter koseri, Burkholderia cепacia (B. cепacia), and Citrobacter freundii (C. freundii) are also sensitive to CFDC with a minimum inhibitory concentration (MIC)90 value of under 1 mg/l (9, 11, 14–16, 19–21). The breakpoints of CFDC have been interpreted by different standards including the Clinical and Laboratory Standards Institute (CLSI), the FDA, and the European Committee on Antimicrobial Susceptibility Testing (EUCAST). The breakpoints of CLSI are commonly used and available for Enterobacteriaceae, A. baumannii, P. aeruginosa, and S. maltophilia (susceptible ≤ 4 mg/l, intermediate 8 mg/l, and resistant ≥ 16 mg/l). The breakpoints of the EUCAST for Enterobacteriaceae and P. aeruginosa are susceptible ≤ 2 mg/l and resistant ≥ 2 mg/l (22). The FDA breakpoints for Enterobacteriaceae have been changed from (susceptible ≤ 2 mg/l, intermediate 4 mg/l, and resistant ≥ 8 mg/l) in 2019 to (susceptible ≤ 4 mg/l, intermediate 8 mg/l, and resistant ≥ 16 mg/l) in 2020 and the standard for A. baumannii (susceptible ≤ 1 mg/l and resistant ≥ 4 mg/l) has been added. The breakpoints for P. aeruginosa remain as (susceptible ≤ 1 mg/l and resistant ≥ 4 mg/l). Broth microdilution and disk diffusion methods are both available for different standards.

Although it has not been long since CFDC appears in the market and its indications are limited, CFDC is highly anticipated and acts as a new option for the treatment of various MDR pathogens (23). Recently, a randomized controlled phase-3 trial study has reported that CFDC has similar clinical efficacy to the best available therapy in infections caused by carbapenem-resistant GNB (24). Another study has reported that CFDC is non-inferior to high-dose and extended-infusion meropenem in the treatment of MDR GNB infections (25).

In this study, we aim to review the in-vitro and in-vivo activity of CFDC to evaluate its global effectiveness so far (Supplementary Table 1) and to discuss the potential mechanism of CFDC resistance.

**REPORTS OF IN-VITRO RESISTANCE TO CFDC**

**Resistance Rate in Enterobacterales**

Generally, CFDC has a high activity against Enterobacterales with most of the MIC90 values ≤ 8 mg/l (10, 11, 13–16, 18–21, 26, 27). Mariana et al. have reported a resistance rate of 5% for 335 Enterobacterales isolates according to the CLSI breakpoints, which are originated from the United States, Canada, and Singapore, with an MIC50 value ranging from 0.015 to >64 mg/l and an MIC90 value of 8 mg/l (21). However, the resistance rate shows obvious differences according to different phenotypes of β-lactamases. Based on the Ambler Classification system, β-lactamases are divided into four classes as follows: classes A, C, and D of serine β-lactamases and class B known as metallo-β-lactamases (MBLs). The β-lactamases that confer the reduction of drug sensitivity in Enterobacterales belong to the abovementioned types: two serine-β-lactamase including ESBL and K. pneumoniae carbapenemases (KPCs) and class B [MBL, especially New Delhi metallo-β-lactamases (NDM)]. Several reports have shown that the resistance rate of MBL-producing Enterobacterales is higher compared with non-MBL-producing pathogens (10, 28, 29). Two studies from Europe and the United Kingdom in 2020 have reported that the resistance rate of NDM-positive strains against CFDC is up to 59 and 48.6% (the EUCAST breakpoints), respectively, with an MIC90 value reaching 32 mg/l (10, 28). Two other studies have also reported the widest MIC90 range of CFDC against NDM-positive Enterobacteraeae up to >64 mg/l (3) or 8 mg/l (30) compared with other β-lactamase phenotypes. Following NDM, another type of Verona integron-mediated MBL (VIM)-positive strain exhibits a high resistance of 19.1 and 21%, respectively (10, 28). The resistance rate of CFDC against class A β-lactamase-positive strains and carbapenemases, such as GES, IMI, SME, and TEM enzyme, is relatively lower compared with class B β-lactamase-positive strains (3, 10, 28). An MIC90 value of CFDC against ESBL + porin loss Enterobacterales ranges from 0.125 to 32 mg/l with a resistance rate of 38.5% (28). Studies from Europe have shown that the resistance rate of KPC-producing pathogens to CFDC is 8.9 and 16.4%, respectively, based on the EUCAST breakpoints (10, 28). Similarly, class D β-lactamase OXA-48-positive Enterobacterales show a resistance rate of 7.1 and 11.8%, respectively, with an MIC90 value reaching 8 mg/l (10, 28). However, another study from North America and Europe has shown that all the 75 KPC-positive and 32 OXA-48-positive strains are sensitive to CFDC (30). The class C β-lactamase AmpC-positive strains are susceptible to CFDC with the resistance rate of 0% (28). Meredith et al. have shown that the resistance rates of meropenem non-susceptible (MIC90
The mechanisms and underlying resistance mechanisms of CFDC.
spp., and Citrobacter spp. and will result in a two- or four-time increase of CFDCs MIC90 (18, 20). Although an MIC90 value of C. freundii ranges from ≤ 0.063 to >64 mg/l and the resistance rate is not provided by Naoki et al., an MIC90 value is as low as 0.125 mg/l (29).

*Pseudomonas aeruginosa*

Generally, CFDC shows an excellent bactericidal effect against P. aeruginosa with an MIC90 value of ≤2 mg/l (3, 13–19, 27, 30). MBLs are still correlated to their CFDC resistance. A study from the United Kingdom has reported that the resistance rate of isolates from 11 NDM-positive and 30 IMP-positive *P. aeruginosa* is 54.5 and 20%, respectively, according to the EUCAST breakpoints, with the upper range of an MIC90 value of ≥ 128 mg/l (28). The resistance rate of the class А β-lactamase (GES, PER, and VEB)-producing isolates is relatively high at 10–33.3% (28). However, two European studies have reported that the resistance rates of VIM-, IMP-, NDM-, and GES-positive *P. aeruginosa* are all 0% (10, 30). Although Dobias et al. did not provide the resistance rate against CFDC, an MIC90 value of 2 mg/l reflects the high activity of CFDC against VIM-, IMP-, KPC-, SPM-, or GIM-producing *P. aeruginosa* (27). An MIC90 value of CFDC against carbapenemase-producing *P. aeruginosa* is a little bit higher compared with non-carbapenemase ones (2 vs. 0.5 mg/l) in a German study, with a resistance rate of 9.1 and 0%, respectively (11). A study from the USA has also reported a high MIC90 value of 8 mg/l in carbapenem-resistant strains (20). The activity of CFDC against carbapenem non-susceptible or MDR *P. aeruginosa* remains well, with an MIC90 value of ≤2 mg/l (14, 17, 19, 30).

*Acinetobacter spp.*

Most studies have demonstrated that an MIC90 value of CFDC against non-enzymes-producing *A. baumannii* is <4 mg/l (3, 10, 13, 15, 16, 19, 27, 30, 31). Ceftazidime resistant had little effect on an MIC90 value of CFDC to *A. baumannii* (13). However, one study has reported that an MIC90 value of CFDC to 97 *A. baumannii* isolates is 32 mg/l according to the CLSI breakpoints, with a resistance rate of 33%. The pathogens collected from the United States, Canada, and Singapore from 1996 to 2015 possess one or multiple types of gene expression including blaCMY, blaCTX-M, blaFOX, blaIMI, blaIMP, blaKPC, blaNDM, blaOXA-48-like, blashV, blaSME, and blatem (21). *A. baumannii* resistance is attributed to the production of OXA- or NDM-type enzymes. Moreover, the resistance rate varies according to different phenotypes of OXA enzymes. The resistance rate of CFDC against OXA-23-positive *A. baumannii* is 14.6%, while it is 11.1, 10, and 5.3% for OXA-24/40-positive strains, OXA-58-positive strains, and OXA-51-positive strains, respectively, using non-species special pharmacokinetic-pharmacodynamic (PK-PD) breakpoints (22, 28). Akinobu et al. have demonstrated that the resistance rate of CFDC against OXA-23-positive strains (16.7%) is relatively higher compared with other phenotypes of OXA-positive *A. baumannii* (0%), with the maximum range of an MIC90 value of >32 mg/l (31). Iregui et al. have also reported that the resistance rate of blaOXA-23 *A. baumannii* is 8.8% according to the CLSI breakpoints, with an MIC90 value of 8 mg/l (13). However, Delgado et al. from Spain and Christopher et al. from Europe have reported that the resistance rate of OXA-24/40-positive strains is 12 and 6.8%, respectively, which is higher compared with other phenotypes (10, 15). A study from the United Kingdom has demonstrated that 20 NDM-producing pathogens show the highest resistance of 50% based on non-species special PK-PD breakpoints, with an MIC90 value ranging from 1 to ≥128 mg/l (22, 28) (since no MIC90 criteria have been provided for CFDC to *A. baumannii*). A Chinese study has reported that the resistance rate of imipenem-resistant pathogens is 7% in 2020 using the CLSI breakpoints, with an MIC90 value ranging from 0.06 to >64 mg/l and an MIC90 value of 8 mg/l (17). Other studies have also shown that carbapenem-resistant strains are more resistant to CFDC compared with the susceptible strains, with a slightly higher MIC90 value or MIC90 range (3, 19, 31). MDR *A. baumannii* exhibits the highest resistance with an MIC90 value of 8 mg/l and an MIC90 range reaching >256 mg/l (18). Two studies have compared an MIC90 value between the isolates from Europe and North America and no significant difference has been found (16, 19).

According to the CLSI breakpoints, Kenneth et al. have shown that the resistance rate of *Acinetobacter spp.* is 10%, with an MIC90 value of 4 mg/l (9). However, CFDC has high activity against *Acinetobacter pittii* from North America and Europe, reported by James et al., with the resistance rate of 0% and an MIC90 value of 0.5 mg/l (16).

**Other Strains**

For S. maltophilia, B. cepacia complex, Morganellaceae, Achromobacter xylosoxidans, and Proteus mirabilis, they show excellent susceptibility to CFDC, with a resistance rate of 0% and an MIC90 value of <1 mg/l, as reported by worldwide studies (11, 14–21, 26).

**REPORTS OF IN-VIVO RESISTANCE TO CFDC**

Several animal studies demonstrated that strains carrying KPC or NDM may reduce the susceptibility to CFDC. An in-vivo study using neutropenic murine thigh and lung infection models has shown that an MIC90 of NDM-producing GNB including *E. coli, K. pneumoniae*, and *P. aeruginosa* was 8- to 64-fold higher than non-producing strains (32). The MIC90 of NDM-1-producing *K. pneumoniae* sequence type 14 (ST14) reach to 16 mg/l, which is resistant to CFDC (32). The MIC90 of KPC-producing pathogens is 16 times higher than non-producing *K. pneumoniae* (4 vs. 0.25 mg/l) (32). In a immunocompetent rat respiratory tract infection model, an MIC90 value at 8 mg/l of NDM-1-positive *K. pneumoniae* is two times higher than KPC-2-positive *K. pneumoniae* (33). In in-vivo models, the amount of inoculation will also affect the MIC90 of CFDC. An MIC90 value at 16–64 mg/l was observed in a *K. pneumoniae* infected neutropenic murine thigh model, which was infected with 10⁷ CFU/ml bacterial suspension (34). According to the EUCAST breakpoints,
Hobson et al. have also reported that high inocula (10⁷ CFU/ml) with KPC-producing Enterobacteriaceae will lead the resistance to CFDC compared to usual inocula (10⁵ CFU/ml) in 2021 (35).

Grande et al. have reported that a 63-year-old male patient with septic shock is presented at the intensive care unit (ICU) due to the initial infection of ESBL K. pneumoniae, oxacillin-sensitive Staphylococcus aureus, and multi-sensitive P. aeruginosa. Then, a VIM-producing XDR P. aeruginosa grows from his sputum on day 26 (36). On day 54, the regimen of colistin and meropenem is switched to CFDC 2 g q8h infused over 3 h plus metronidazole 500 mg TID as P. aeruginosa is susceptible to CFDC. The treatment regimen is discontinued after 6 weeks (36). On day 128, GES- and VIM-producing XDR P. aeruginosa are isolated from ischial eschar with an MIC90 value of CFDC increased to 8 mg/l (36). It indicates that P. aeruginosa develops resistance during CFDC treatment.

RESISTANCE MECHANISMS

Previous studies have shown that the presence of single-type MBLs may increase an MIC90 value of CFDC against part of the isolates. However, one study has demonstrated that the co-expression of MBLs and serine-type β-lactamases is related to the non-susceptibility of CFDC (37). An MIC90 value to CFDC presents an 8- to 64-fold and 8-fold reduction against CFDC-resistant Enterobacterales (including E. coli and K. pneumoniae) and A. baumannii, respectively, when both the dipicolinic acid (an MBL inhibitor) and avibactam (a serine-β-lactamase inhibitor) are added to the susceptible level (≤0.5 μg/ml) (37). However, an MIC90 value of ≤ 2-fold for CFDC has not been observed by the addition of dipicolinic acid or avibactam alone (37). Mutations in β-lactamases may also lead to CFDC resistance (Figure 1). A 4- to 32-fold increase of an MIC90 was observed in D179Y-H274Y mutations of KPC-31 compared to the wild-type alleles reported by Hobson et al. in 2021 (35). Shields et al. have reported that the deletion of positions 292 and 293, which are located in the R2 loop of AmpC, causes the decreased susceptibility of Enterobacterales (38). The mutations lead to the disappearance of the H10 helix in the R2 loop and the expansion of the substrate-binding site, resulting in a more stable binding to the bulkier side chain possessed by CFDC (38). Akito et al. have demonstrated the alanine-proline deletion at positions 294 and 295 located in the R2 loop, which is also associated with the reduced susceptibility to CFDC in E. coli and E. cloacae (39). Especially for E. cloacae, the deletion of A294_L295 results in an increase of >32-fold in an MIC90 value of CFDC (39).

TonB-dependent receptors commonly exist in GNB outer membrane and assist CFDC to enter the bacterial periplasmic space via cooperation with the TonB-ExbB-ExbD complex located in the cytoplasmic membrane (40). The energy required for the transport of CFDC is provided by TonB-ExbB-ExbD complex (40). The main TonB-dependent receptors of A. baumannii are termed as PiuA and PirA (41). Malik et al. have reported that the change from a hydrophobic amino acid to an aromatic amino acid at location 275 of PirA and the downregulation of pirA, possibly in combination with loss of piuA, cause the decreased expressions of TonB-dependent receptors, which interpret the increased resistance to CFDC in A. baumannii (42) (Figure 1). Decreased sensitivity to CFDC has also been observed in P. aeruginosa when the loss of piuA and downregulation of TonB-dependent receptors occur (41) (Figure 1). Alexandre et al. have shown that the decreased expression of PiuA ortholog, termed as PiuD, which is encoded by piuD, is more important than the loss of piuA (43). They had tested an MIC90 value of P. aeruginosa when piuA or piuD is depleted and found that the deletion of piuA increases the CFDC MIC90 value by 2-fold, while such elevation for the deletion of piuD is 32-fold (43). Moynié et al. have considered that TonB3-ExbB3-ExbD3 complex not only provides energy for the siderophore transport, but also is associated with siderophore acquiring Fp34-42. Mutation of TonB3-ExbB3-ExbD3 by insertion of A at position 9 in the exbD3 gene, deletion of A at position 319, and insertion of A at position 243 in the tonB3 gene would impede energy acquisition for transport and iron availability. Therefore, the transmission of CFDC to bacteria would be inhibited (41).

CONCLUSION

In conclusion, CFDC has demonstrated excellent activity against GNB including ESBL Enterobacterales, CRE, MDR A. baumannii, and carbapenem-resistant P. aeruginosa. The expressions of MBLs are associated with the decreased sensitivity of pathogens to CFDC. However, the acquisition of a particular β-lactamase does not ensure resistance and additional mechanisms such as mutations in β-lactamases are necessary for overt resistance to develop. Moreover, since the CFDC resistance has already been reported during its anti-infective therapy, the clinical application needs to be cautious to preserve the activity of CFDC.

AUTHOR CONTRIBUTIONS

JY wrote the first draft of the manuscript. JW, MC, and YC contributed to manuscript revision. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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30. Kazmierczak KM, Tsuji M, Wise MG, Hackel M, Yamano Y, Echols R, et al. 
In vitro activity of cefiderocol, a siderophore cephalosporin, against a recent 
collection of clinically relevant carbapenem-non-susceptible Gram-negative 
bacilli, including serine carbapenemase- and metallo-β-lactamase-producing 
isolates (SIDERO-WT-2014 Study). Int J Antimicrob Agents. (2019) 53:177– 
84. doi: 10.1016/j.ijantimicag.2018.10.007
31. Ito A, Kohira N, Bouchillon SK, West J, Rittenhouse S, Sader HS, et al. In 
vitro antimicrobial activity of S-649266, a catechol-substituted siderophore 
cephalosporin, when tested against non-fermenting Gram-negative bacteria. 
J Antimicrob Chemother. (2016) 71:670–7. doi: 10.1093/jac/dkv402
32. Nakamura R, Ito-Horiyama T, Takemura M, Toba S, Matsumoto S, 
Ikehara T, et al. In vivo pharmacodynamic study of cefiderocol, a 
novel parenteral siderophore cephalosporin, in murine thigh and lung 
fection models. Antimicrobial Agents Chemother. (2019) 63:e02031–18. 
doi: 10.1128/AAC.02031-18
33. Matsumoto S, Singley CM, Hoover J, Nakamura R, Echols R, Rittenhouse 
S, et al. Efficacy of cefiderocol against carbapenem-resistant gram-negative 
bacilli in immunocompetent-rat respiratory tract infection models recreating 
human plasma pharmacokinetics. Antimicrobial Agents Chemother. (2017) 
61:e00700–17. doi: 10.1128/AAC.00700-17
34. Monogue ML, Tsuji M, Yamano Y, Echols R, Nicolau DP. Efficacy of 
humanized exposures of cefiderocol (S-649266) against a diverse population 
of gram-negative bacteria in a murine thigh infection model. Antimicrobial 
Agents Chemother. (2017) 61:e01022–17. doi: 10.1128/AAC.01022-17
35. Hobson CA, Cointe A, Jacquier H, Choudhury A, Magnan M, Courroux C, 
et al. Cross resistance to cefiderocol and ceftazidime-avibactam in KPC 
β-lactamase mutants and inoculum effect. Clin Microbiol Infect. (2021) 2021:16. 
doi: 10.1016/j.cmi.2021.04.016
36. Grande Perez C, Maillard E, Mienda Deyi VY, Huang TD, Kamgang P, 
Dernier Y, et al. Compassionate use of cefiderocol in a pancreatic abscess 
and emergence of resistance. Médecine et Maladies Infectieuses. (2020) 2020:22. 
doi: 10.1016/j.medmal.2020.10.022
37. Kohira N, Hackel MA, Ishioka Y, Kuroiwa M, Sahm DF, Sato T, et al. Reduced 
susceptibility mechanism to cefiderocol, a siderophore cephalosporin, among 
clinical isolates from a global surveillance programme (SIDERO-WT-2014). J 
Glob Antimicrob Resist. (2020) 22:738–41. doi: 10.1016/j.jgarr.2020.07.009
38. Shields RK, Iovleva A, Kline EG, Kawai A, McElheny CL, Doi Y. 
Clinical evaluation of AmpC-mediated ceftazidime-avibactam and cefiderocol 
resistance in Enterobacter cloacae complex following exposure to cefepime. 
Clin Infect Dis. (2020) 71:2713–6. doi: 10.1093/cid/ciaa355
39. Kawai A, McElheny CL, Iovleva A, Kline EG, Sluis-Cremer N, Shields RK, 
et al. Structural basis of reduced susceptibility to ceftazidime-avibactam 
and cefiderocol in Enterobacter cloacae due to AmpC R2 loop deletion. 
Antimicrob Agents Chemother. (2020) 64:20. doi: 10.1128/AAC.00198-20
40. Hartney SL, Mazurier S, Girard MK, Mehnaz S, Davis EW 2nd, Gross H, et al. Ferric-pyoverdine recognition by Fpv outer membrane 
proteins of Pseudomonas protegens Pf-5. J Bacteriol. (2013) 195:765–76. 
doi: 10.1128/JB.01639-12
41. Moynié L, Luscher A, Rolo D, Pletzer D, Tortajada A, Weingart H, et al. 
Structure and function of the PiuA and PirA siderophore-drug receptors from 
Pseudomonas aeruginosa and Acinetobacter baumannii. Antimicrob Agents 
Chemother. (2017) 61:16. doi: 10.1128/AAC.02531-16
42. Malík S, Kaminski M, Landman D, Quale J. Cefiderocol resistance in 
Acinetobacter baumannii: roles of β-lactamases, siderophore receptors, and 
penicillin binding protein 3. Antimicrob Agents Chemother. (2020) 64:20. 
doi: 10.1128/AAC.01221-20
43. Luscher A, Moynié L, Auguste PS, Bumann D, Mazza L, Pletzer D, et al. 
TonB-dependent receptor repertoire of Pseudomonas aeruginosa for uptake 
of siderophore-drug conjugates. Antimicrob Agents Chemother. (2018) 62:18. 
doi: 10.1128/AAC.00097-18

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