**Figure 1: Study flowchart**

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\* Three of the 34 *in vitro*  studies also include an *in vivo*  model, therefore, in total, studies assessing *in vivo* activity of cefiderocol are 5.

**Table 1. Summary of cefiderocol *in vitro* synergisms**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Author, year** | **Molecules** | **Methods** | **Isolates** | **Synergy** | **Result** |
| Tsuji, 2016 | MER, AMK, and COL | BMD MIC | 41 EB, 20 *Pa*, and 21 *Ab* resistant to meropenem | Synergy for MER (11% *Pa*, 26% EB and 43% *Ab*) |  |
| MER, AMK, and CIP | Checkerboard and time-kill | 1 FDC-R KPC-*Kp*, 1 VIM-10-*Pa, and* 1 FDC-R MDR-*Ab* | Synergy for MER in *Kp* and AMK in *Ab* |  |
| Palombo, 2023 | P–T, FOS, A–S, CZA, MEV, and IMR | Gradient diffusion strip crossing | FDC-R: 1 *Kp* and 1 *Ab*  FDC-S: 1 *Kp*, 1 *Ab*, and 2 *Pa* | No synergy for P/T, MEV, IMR  R: synergy for FOS (n=2) and CZA in 1 *Kp;* S: synergy for CZA in 1 *Pa* and A-S in 1 *Pa* |  |
| Kohira, 2020 | AVI | BMD MIC | 33 non-NDM-EB, *Ab*, and *Pa* | ≥8-fold MIC decrease in 32/33 |  |
| Le Terrier, 2024 | ZID, TAN, NAC, AVI, REL, VAB | BMD MIC | 67 EB, 9 *Pa* and 11 *Ab* | EB and *Pa*: FDC+ZID showed the highest susceptibility rate, other combinations had lower rates  *Ab*: FDC+ZID, AVI, TAN or REL had susceptibility rates >90% (FDC alone 9.1%) |  |
| Xu, 2025 | ZID | Checkerboard | 14 FDC-R-EB+  FDC-S-*Ab* | ZID restored and even enhanced FDC antibacterial activity |  |
| Time-kill | 8 FDC-R-EB+  FDC-S-*Ab* | FDC+ZID inhibited the growth of all strains (FDC did not achieve it) |  |
| Cell infection model | 1 FDC-R-*Ent. cloacae* | FDC+ZID: significant reduction in the number of viable intracellular bacteria |  |
| Hara, 2024 | XER | BMD MIC | 160 FDC-R and S-*Ab* | XER significantly improved FDC activity |  |
| Hara, 2024 | XER | BMD MIC | 165 EB (139 CRE) | XER significantly improved FDC activity |  |
| Yamano, 2019 | CZA, TOL-TAZ, and MER | BMD MIC, checkerboard, time-kill, chemostat | 9 EB (5 NDM), and 28 *Ab* (25 PER), all FDC-R | CZA, TOL-TAZ and MER synergic against non-NDM isolates (including PER-producing *Ab)* |  |
| Lewis, 2024 | AVI, SUL, TAZ | Time-kill | 2 *Kp*, 2 *Pa* and 2 *Ab*  (FDC-R and S) | SUL enhanced FDC activity in all isolates |  |
| Giordano, 2024 | Glycine | Checkerboard | 5 NDM-*Kp* + 5 *Ab*  (all FDC-R) | Positive interaction but no synergy |  |
| Abdul-Mutakabbir, 2021 | MER, AMK, TGC, MIN, SUL, CZA, and COL | Time-kill | 6 FDC-R *Ab* | No synergy for CZA and COL (in COL-R). Synergy for the other antibiotics |  |
| Ni, 2022 | TGC, COL, and MER | Checkerboard | 123 CRAB (44 FDC-R  and 79 S) | S: synergy for TGC (85%)  R: synergy for TGC (91%), COL (48%), and MER (80%) |  |
| Time-kill | 21 CRAB (14 FDC-R  and 7 S) | S: synergy for TGC (100%)  R: synergy for TGC and COL (100%) |  |
| TGC and COL | *In vivo* model | 4 CRAB (2-FDC-R and 2 S) | S: FDC-TGC increased survival  R: FDC-TGC and FDC-COL increased survival |  |
| Yin, 2024 | TET analogues (MIN, TIG, ERA, OMA) | Checkerboard | 48 FDC-S CRAB | Synergy in 35.4% MIN, 33.3% TIG, 50.0% ERA and 37.5% OMA |  |
| Time-kill | 10 FDC-S CRAB | Synergistic effects in most isolates |  |
| *In vivo* model | 2 FDC-S CRAB | FDC+ERA reduced nearly 2 log10 CFU/thigh |  |
| Stolfa, 2021 | COL, TGC, and FOS | Gradient diffusion strip crossing | 15 FDC-S XDR-*Ab* | No synergy found |  |
| Yamano, 2020 | AVI, SUL, MER, AMK | Checkerboard | 2-FDC-R-PER-*Ab* | Synergy for AVI and SUL |  |
| Bianco, 2022 | TAZ, AVI, VAB, REL | Checkerboard | 39 (9-FDC-R: 4 KPC-*Kp*, 3-NDM-EB and 2 NDM and OXA-23-like-*Ab*) | KPC: synergy for AVI, VAB, REL  MBL: very low synergy with TAZ, AVI, REL  OXA: synergy for TAZ, AVI, VAB, REL in all OXA-48-EB but not for *Ab* |  |
| Time-kill | 4 FDC-S (KPC-3-*Kp*, NDM-1-*Ec*, OXA-23-*Ab*, OXA-48-*Kp*) and 1 FDC-R (KPC-50-*Kp*) | KPC: synergy for AVI, VAB, REL  NDM and OXA-23: no synergy  OXA-48: synergy for TAZ and AVI |  |
| Gopikrishnan, 2023 | ZID and AVI | BMD MIC and molecular simulation | 52 (13 FDC-R) CRAB (OXA‐23, 24, and 58) | Inhibitory activity of FDC+ZID better than monotherapy |  |
| Huband, 2024 | SUL | BMD MIC | 66 *Ab* | Negative |  |
| DUR | Positive |  |
| SUL-DUR | Positive (stronger than only with DUR) |  |
| Kobic, 2022 | SUL and TGC | Time-kill | 1 FDC-S XDR *Ab* | Only synergy for FDC+SUL+TGC |  |
| Wong, 2024 | SUL, AVI | - | 2 FDC-S Ab and A. lwoffii (NDM-1 producers) | Exposure to FDC+SUL or FDC+AVI led to the selection of FDC-R strains |  |
| You, 2025 | - | AI | 1 XDR *Ab* | FDC+A-S and FDC+PM-B+RIF were pinpointed (93.89 ± 5.95% and 92.23 ± 11.89% inhibition) |  |
| A-S, PM-B+RIF | Checkerboard | 4 *Ab* | FDC+PM-B+RIF showed synergy but FDC+A-S antagonism |  |
| Bianco, 2022 | CZA | Gradient diffusion strip crossing | 4 (1 FDC-R) KPC+VIM-EB,  4 (1 FDC-R) NDM+OXA-48 like-EB and 2 (both FDC-S) VIM+OXA-48 like-EB | No synergy |  |
| Göpel, 2024 | ATM | Checkerboard | 20 NDM-*Ent. cloacae* | Synergy found |  |
| Bianco, 2022 | CZA, MEV, IMI, and AMK | Gradient diffusion strip crossing | 6 (3 FDC-R and 3 S)  KPC-*Kp* | Synergy for CZA (synergy rate of 67%) |  |
| Boattini, 2022 | CZA | Gradient diffusion strip crossing | 2-VIM*-Pa* and 3 NDM-*Kp* | Synergy in 1 NDM-*Kp* and only additive effects in 1 NDM-*Kp* and 1 VIM-*Pa* |  |
| Moon, 2023 | AVI | Double-disk assay | 1 FDC-R *Kp* | AVI enhanced the activity of cefiderocol |  |
| Daoud, 2023 | AVI, TAZ, SUL, CA, DPA, PMBN | Checkerboard | 34 *Kp* | Synergy with AVI (highest), TAZ, SUL, CA AND PMBN  DPA: non-significant improvement  FDC+AVI+DPA: significant reduction  FDC+AVI+PMBN: not statistically significant effect compared to FDC+AVI |  |
| AVI, PMBN | Time-kill | 4 *Kp* | FDC+AVI enabled the killing of the bacteria earlier with a lower concentration of FDC  FDC+AVI+PMBN: bacterial killing at lower concentrations of FDC and less time than FDC+AVI |  |
| Daoud, 2023 | AVI, DPA, ATM | Checkerboard | 1 FDC-R *Kp* | FDC+AVI: no synergy  FDC+DPA: synergy  FDC+AVI+(ATM or DPA): synergy |  |
| Granata, 2025 | IMR | Gradient diffusion strip crossing | 3 FDC-S (2 IMP-13 and 1 VIM-2-*Pa*) | Synergy in 2 IMP-13-*Pa* (not in VIM-2-*Pa)* |  |
| Ferretti, 2024 | IMI | Minimum biofilm bactericidal concentration (≈ BMD MIC) | 5 FDC-S *Pa* | Synergistic bactericidal activity in all tested strains and synergistic eradicating activity in one isolate |  |
| El Haj, 2024 | COL | *In vitro* pharmacodynamic model | 2 FDC-S *Pa* | COL improved FDC efficacy against biofilms |  |
| Schilling, 2024 | VAN | Gradient diffusion strip crossing | 2 FDC-S *Pa* | Indifferent |  |
| Wang, 2023 | CBS | BMD MIC | *Pa and B. cepacia* | Synergy found |  |
| Checkerboard and time-kill | *Pa* | Synergy found |  |
| *In vivo* model | *Pa* | FDC-CBS significantly increased survival |  |
| Biagi, 2020 | LEV, MIN, PM-B, SXT | Time-kill | 9-FDC-S  *S. maltophilia* | Synergy found (44% LEV, 67% MIN, 56% PM-B and 67% SXT) |  |
| **Molecules** (in alphabetical order) AMK: amikacin, A-S: ampicillin-sulbactam, ATM: aztreonam, AVI: avibactam, CA: clavulanic acid, CBS: colloidal bismuth citrate, CIP: ciprofloxacin, COL: colistin, CZA: ceftazidime-avibactam, DPA: dipicolinic acid, DUR: durlobactam, ERA: eravacycline, FDC: cefiderocol, FOS: fosfomycin, IMI: imipenem, IMR: imipenem-relebactam, LEV: levofloxacin, MER: meropenem, MEV: meropenem-vaborbactam, MIN: minocycline, NAC: nacubactam, OMA: omadacycline, PM-B: polymyxin B, PMBN: polymyxin B nonapeptide, P–T: piperacillin-tazobactam, REL: relebactam, RIF: rifampicin, SUL: sulbactam, SXT: cotrimoxazole, TAN: taniborbactam, TAZ: tazobactam, TGC: tigecycline, TOL-TAZ: ceftolozane-tazobactam, VAB: vaborbactam, VAN: vancomycin, XER: xeruborbactam and ZID: zidebactam.  **Methods and isolates** (in alphabetical order) Ab: *Acinetobacter baumannii* complex, BMD MIC: broth microdilution minimal inhibitory concentration, CRAB: carbapenem-resistant *Acinetobacter baumannii complex*, CRE:carbapenem-resistant Enterobacterales, EB: Enterobacterales, Ec: *Escherichia coli*, MBL: metallo ß-lactamase, Pa: *Pseudomonas aeruginosa*, Kp: *Klebsiella pneumoniae*, R: resistant and S: susceptible.  **Results**: green: positive synergy, red: no synergy and yellow: variable synergy. | | | | | |

**Table 2. Summary of cefiderocol combination therapies in human studies**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author, year** | **Type of study** | **Infection type** | **Pathogen(s)** | **Number of patients treated with cefiderocol** | **Combination therapies** | **Microbiological outcome** | **Clinical**  **outcome** |
| Bassetti, 2020 | Clinical trial | Pneumonia  BSIs, cUTI | CRAB  *Kp,* *Pa,*  *S. maltophilia* | 80  Mono: 66 (83%)  Combo: 14 (18%) | TGC, FOS, AMK, A-S, CIP, COL, GEN, LEV, P-T | Eradication  Mono: 32%  Combo: 29%  P=NS | Clinical cure  Mono: 53%  Combo: 50%  P=NS |
| Dalfino, 2023 | P | VAP | CRAB | 40  Mono: 19 (48%)  Combo: 21 (53%) | FOS, aerosolized COL | N/A | Clinical cure  Mono: 18%  Combo: 36%  P N/A |
| Buonomo,  2024 | P | VAP, BSIs, CLABSI | CRAB | 23  Mono: 11 (48%)  Combo:12 (52%) | A-S, FOS, TGC | N/A | Clinical cure  Mono: 56%  Combo: 44%  P=NS |
| Giacobbe,  2024 | P | LRTI, BSIs, SSTI, cIAI | CRAB, *Pa, E*, SMAL | 200  Mono: 101(51%)  Combo 99 (50%) | FOS, TGC, A-S, COL, AGs | N/A | N/A |
| Falcone,  2022 | R | BSIs, VAP | CRAB | 47  Mono: 15 (32%)  Combo: 32 (68%) | TGC, FOS, ERT, M-V,  A-S | Failure  Mono 40%  Combo: 6% P<0.01 | N/A |
| Mazzitelli, 2023 | R | BSIs Pneumonia  IAIs, cUTIs | CRAB | 60  Mono: 30 (50%)  Combo: 30 (50%) | MER; TGC, FOS | Cure  Mono: 50%  Combo: 37%  P=0.03 | Clinical cure  Mono: 33%  Combo: 53%  P=NS |
| Russo, 2023 | R | VAP with BSIs11 | CRAB | 19  Mono: 0 (0%)  Combo: 19 (100%) | TGC, FOS, TMP/SMX,  A-S | N/A | 30-day survival higher for cefiderocol-based regimens (HR 0.34, 95% CI 0.18–0.56; P < 0.001) and cefiderocol + fosfomycin (HR 0.22, 95% CI 0.1–0.55; P < 0.001) |
| Bavaro, 2023 | R | BSIs | CRAB | 43  Mono: 16 (37%)  Combo: 27 (63%) | FOS,  A-S | Resistance development  Mono: 13%  Combo: 0%  P N/A | 30-day mortality similar in mono vs. combo  (HR = 0.81, 95% CI 0.39–1.66) and lower for cefiderocol + fosfomycin (HR = 0.43, 95% CI 0.22–0.81) |
| Piccicca,  2023 | R | BSIs, VAP  IAIs, UTIs | CRAB  *Kp*  *Pa* | 142  Mono: 70 (49%)  Combo: 72 (51%) | FOS,  A-S | Cure  Mono: 46% Combo: 52%  P N/A | 30-day mortality  Mono: 33%  Combo: 40%  P=NS |
| Palermo,  2023 | R | HAP, BSIs  cUTIs, cIAIs  SSTIs | CRAB  *Kp*  *Pa* | 41  Mono: 31 (76%)  Combo: 10 (24%) | FOS, COL | Cure  Mono: 87% Combo: 60%  P N/A | Clinical cure  Mono: 58%  Combo: 50%  30-day mortality  Mono: 36%  Combo: 40%  P=NS |
| Calò,  2023 | R | Pneumonia  CLABSI | CRAB | 40  Mono: 29 (73%)  Combo: 11 (28%) | A-S, FOS, TGC,  AMK | Failure  Mono: 14%  Combo: 0%  P N/A | Clinical cure  Mono: 42%  Combo: 64%  30-day mortality  Mono: 52%  Combo: 46%  P=NS |
| Giannella, 2023 | R | VAP, BSIs  CLABSI | CRAB | 147  Mono: 49 (33%)  Combo: 98 (67%) | FOS, COL, TGC, MER,  A-S | N/A | Clinical cure  Mono: 61%  Combo: 49%  28-day survival  Mono: 53%  Combo: 41%  P N/A |
| Gavghan,  2023 | R | Pneumonia | CRAB  *Pa* | 24  Mono: 16 (67%)  Combo: 8 (33%) | TGC, GEN, COL, TOB, MIN | N/A | Clinical cure  Mono 56%  Combo: 25%  P N/A |
| Monirul, 2023 | R | LRTI,SSTIs, BJI,Bsi,cUTI, cIAIs | CRAB, *Pa* | 22  Mono 10 (45%)  Combo 12 (55%) | N/A | N/A | 28-day mortality  Mono: 25%  Combo: 0% |
| Frattari, 2024 | R | Sepsis | CRAB | 36  Mono:16(44%)  Combo 22(61%) | N/A | N/A | 30 day mortality  Mono:56%  Combo: 50% |
| Oliva, 2024 | R | BSIs, VAP, CLABSI, HAP | CRAB | 50  Mono: 14(28)  Combo: 36(72%) | A-S, FOS, TGC, MER | N/A | N/A |
| El Ghali, 2024 | R | VAP, HAP, SSSI, cIAIs, cUTI, BJI | CRAB, *Pa, Kp* | 112  Mono: 39 (35%)  Combo: 73 (65%) | COL, CZA-AVI, AGs, ERAV, IMI-REL, CEP, A-S | Cure.  Mono: 78%  Combo: 82% | 30 day mortality  Mono:18%  Combo:82%  Clinical cure  Mono: 64%  Combo: 35% |
| Clancy,  2024 | R | LRTI, SSSI BSIs, cUTI, cIAIs, BJI, other, | CRAB, *Pa, E,* SMAL, other | 244  Mono:130(53%)  Combo: 114(47%) | N/A | N/A | N/A |
| Russo, 2024 | R | VAP, BSIs, CLABSI, other | CRAB | 54  Combo: 54 (100%) | FOS | N/A | Clinical cure  Combo: 77% |
| Balandin, 2024 | R | LRTI, SSTI, cIAIs,cUTI, BSIs, CLABSI, BJI | *Pa, E, Kp,* CRAB, SMAL | 63  Combo; 33(52%)  Mono: 30 (48%) | COL, other | N/A | N/A |
| Soueges, 2024 | R | LRTI, BSIs, cUTI, | *Pa,E,*Other | 114  Combo 58(51%)  Mono: 56(49%) | N/A | N/A | 28 day mortality  Mono:34%  Combo:41%  Clinical cure  Mono: 55%  Combo:52% |
| Gatti, 2021 | Case series | BSis, VAP | XDR CRAB | 13  Mono:3(23%)  Combo (67%) | A-S, FOS, COL | Failure  Mono: 1/3(33%)  Combo: 5/10 (50%) | 30 day mortality  Mono: 2/3 (66%)  Combo: 2/10 (20%) |
| Rando,  2021 | Case series | VAP | CRAB | 13  Mono: 8 (62%)  Combo: 5 (39%) | COL, FOS | N/A | Clinical cure  Mono: 75%  Combo: 20%  P N/A |
| Corcione,  2022 | Case series | VAP | CRAB,  *S.maltophilia*  *Kp* | 18  Mono: 4 (22%)  Combo: 14 (78%) | TGC, aerosolized COL | Failure  Mono: 25% Combo: 21% | Clinical cure:  Mono: 75%  Combo: 64%  30-day mortality  Mono: 25%  Combo: 29%  P N/A |
| Smoke, 2022 | Case series | BSIs, VAP, LRTI | CRAB | 11  Combo:3(28%)  Mono 8(72%) | POL | N/A | Clinical cure  Mono:2/3(66%)  Combo: 2/9(22%)  30-day mortality  Mono 1/3 (33%)  Combo 1/9/(11%) |
| Wicky,  2023 | Case series | BSIs | CRAB, *Pa,*  *S. maltophilia* | 16  Mono: 11 (69%)  Combo: 5 (31%) | COL, FOS, TGC | N/A | Clinical cure  Mono: 82%  Combo: 80%  P N/A |
| De la Fuente,  2023 | Case series | HAP, VAP | *Pa*  *Burkholderia cepacia*  *Kp*  *S. maltophilia* | 13  Mono: 6 (46%)  Combo: 7 (54%) | COL, CIP, LEV, CAZ, MER | Cure 13/13 (100%) mono and 6/7 (86%) combo | Clinical cure  Mono: 92%  Combo: 86%  P N/A  28-day mortality  Mono: 8%  Combo: 28%  P N/A |
| Meschiari,  2021 | Case series | VAP/HAP  cIAIs, EVD-meningitis,  BSIs | *Pa* | 17  Mono:3 (18%)  Combo: 14 (82%) | Aerosolized COL, FOS, CAZ-AVI, AMK | Failure 2/3 (66%) mono and  2/14 (14%) combo | Clinical failure day 7  Mono: 28%  Combo: 0%  P N/A |
| Fendian,  2023 | Case series | VAP, BSIs | CRAB  *Pa*  *Achromobacter xylooxidans* | Total: 10  Mono: 3 (33%)  Combo: 7 (67%) | COL, TGC, LEV, CAZ-AVI, CEP | Microbiological resistance 1/3 (33%) mono and 1/7 (14%) combo | Clinical failure day 7  Mono: 0%  Combo: 14%  P N/A  90-day mortality  Mono: 33%  Combo: 50%  P N/A |
| Campogiani,  2023 | Case series | BSIs, VAP, cUTI, IAI | CRAB | Total: 11  Mono: 3/11 (27%)  Combo: 8/11 (73%) | COL, TGC | Breakthrough infections:  -Mono: 0/3 (0%)  -Combo: 1/8 (12.5%)  P: N/A  Microbiological relapse:  -Total: 0/11 (0%)  -Mono: 0/3 (0%)  -Combo: 0/8 (0%)  P: N/A | Early clinical improvement:  -Mono: 2/3 (66.67%)  -Combo: 6/8 (75%)  P: N/A  Clinical cure  -Mono: 2/3 (66.67%)  -Combo 6/8 (75%)  P: N/A  Overall 30 day mortality:  -Mono: 1/3 (33.3%)  -Combo: 2/8 (25%)  P: N/A |
| Persuad,  2024 | Case series | HAP/VAP | Pa, E | Total: 15  Mono: 3/15 (20%)  Combo 12/15 (80%) | COL, CAZ-AVI, AMK, POL | Cure  -Total: 9/15 (60%)  -Mono: 2/3 (66.6%)  -Combo: 7/12 (58%)  P: N/A  Resistance:  -Totale: 1/15 (7%)  -Mono: 0/3 (0%)  -Combo: 1/12 (8%)  P: N/A | 30 day- mortality:  -Mono: 1/3 (33%)  -Combo: 3/12 (25%)  P: N/A |
| Travi,  2024 | Case series | VAP, BSI, BJI | CRAB (100% NDM) | Total: 12  Mono: 2/12 (17%)  Combo: 10/12 (83%) | COL | N/A | Clinical cure day-7:  -Mono: 1/2  -Combo: 9/10  P: N/A |
| AMK: amikacin, A–S: ampicillin-sulbactam, CEP: cefepime, CIP: ciprofloxacin, COL: colistin, CAZ: ceftazidime, CZA-AVI: ceftazidime-avibactam, FOS: fosfomycin, LEV: levofloxacin, MER: meropenem, MIN: minocycline, M-V: meropenem-vaborbactam, P–T: piperacillin-tazobactam, TMP/SMX: trimethoprim/sulfamethoxazole, TGC: tigecycline, TOB: tobramycin, AGs: aminoglycosides, ERAV: eravacycline, IMI-REL: imipenem/cilistatin/releabactam. POL = polymixin. CRAB: carbapenem-resistant *Acinetobacter baumannii* complex, *Pa*: P. aeruginosa; *Kp*: K. pneumoniae; E:Enterobacteriales; SMAL: Stenotrophomonas maltophilia;XDR: extensively-drug resistant.  P: prospective study; R: retrospective study; Combo: combination. BSIs: bloodstream infection; CLABSI: central line associated BSIs; LRTI: lower respiratory tract infections; SSTI: skin and soft tissue infections; cIAIs: complicated intra-abdominal infection; cUTIs: complicated urinary tract infection; EVD extra ventricular drainage; HAP: hospital acquired pneumonia; VAP: Ventilator-Associated Pneumonia, BJI: bone and joint infections. NS: non-significant  P values not reported or calculated by the authors are reported as N/A. | | | | | | | |

**Figure 2. Main results and limitations of *in vitro*, *in vivo*, and human studies.**  **BLIs: Beta-lactamase inhibitors**

