# SUPPLEMENTAL MATERIAL

**Table S1.** MEDLINE and EMBASE search strings.

|  |  |  |
| --- | --- | --- |
| **#** | **Searches** | **Results** |
| 1 | exp urinary tract infection/ or exp Pyelonephritis/ or exp Catheter-Related Infections/ or (urinary tract infection$ or uti or utis).tw. or pyelonephr$.tw. or bacteriuria$.tw. or (catheter$ adj2 infection$).tw. or ((genitourin$ or ureter$ or ureth$ or urin$ or urolog$ or urogen$ or catheter) adj5 (infect$ or bacteria$ or microbiol$ or abcess$)).tw. or (urin$ adj5 (abnormal$ or obstruct$ or fistula$ or calcul$ or stricture$)).tw. | 293375 |
| 2 | (amikacin$ or amoxicillin$ or ampicillin$ or aztreonam$ or cefepime$ or (cefiderocol$ or S-649266 or GSK-2696266) or cefoperazone$ or cefotaxime$ or ceftazidime$ or ceftibuten$ or ceftolozane$ or ceftriaxone$ or ciprofloxacin$ or colistin$ or colistimethate sodium or doripenem$ or (eravacycline$ or TP-434) or ertapenem$ or faropenem$ or fosfomycin$ or gentamicin$ or imipenem$ or levofloxacin$ or meropenem$ or minocycline$ or netilmicin$ or piperacillin$ or (plazomicin$ or ACHN-490) or polymixin$ or prulifloxacin$ or temocillin$ or ticarcillin$ or tobramycin$ or trimethoprim$ or (Relebactam$ or MK-7655)).tw. | 302966 |
| 3 | Clinical trial/ or Randomized controlled trial/ or Randomization/ or Single blind procedure/ or Double blind procedure/ or Crossover procedure/ or Placebo/ or Randomi?ed controlled trial$.tw. or Rct.tw. or Random allocation.tw. or Randomly allocated.tw. or Allocated randomly.tw. or (allocated adj2 random).tw. or Single blind$.tw. or Double blind$.tw. or ((treble or triple) adj blind$).tw. or Placebo$.tw. or Prospective study/ or Randomized Controlled Trials as Topic/ or randomized controlled trial/ or Random Allocation/ or Double Blind Method/ or Single Blind Method/ or clinical trial/ or clinical trial, phase ii.pt. or clinical trial, phase iii.pt. or clinical trial, phase iv.pt. or controlled clinical trial.pt. or randomized controlled trial.pt. or multicenter study.pt. or clinical trial.pt. or exp Clinical Trials as topic/ or (clinical adj trial$).tw. or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. or PLACEBOS/ or placebo$.tw. or randomly allocated.tw. or (allocated adj2 random$).tw. | 4322791 |
| 4 | case report.tw. or letter/ or historical article/ or Case study/ or Case report.tw. or Abstract report/ or letter/ or Case study/ or Case report.tw. or Abstract report/ or letter/ | 4725669 |
| 5 | animal/ | 7817145 |
| 6 | human/ | 37234314 |
| 7 | 5 and 6 | 2233463 |
| 8 | 5 not 7 | 5583682 |
| 9 | 4 or 8 | 10218965 |
| 10 | 3 not 9 | 4073139 |
| 11 | 1 and 2 and 10 | 5209 |
| 12 | limit 11 to (english language and yr="2017 -Current") | 559 |
| 13 | remove duplicates from 12 | 435 |

**Table S2.** COCHRANE LIBRARY (CENTRAL and CDSR) search strings.

|  |  |  |
| --- | --- | --- |
| **#** | **Searches** | **Results** |
| 1 | exp urinary tract infection/ or exp Pyelonephritis/ or exp Catheter-Related Infections/ or (urinary tract infection$ or uti or utis).tw. or pyelonephr$.tw. or bacteriuria$.tw. or (catheter$ adj2 infection$).tw. or ((genitourin$ or ureter$ or ureth$ or urin$ or urolog$ or urogen$ or catheter) adj5 (infect$ or bacteria$ or microbiol$ or abcess$)).tw. or (urin$ adj5 (abnormal$ or obstruct$ or fistula$ or calcul$ or stricture$)).tw. | 10994 |
| 2 | (amikacin$ or amoxicillin$ or ampicillin$ or aztreonam$ or cefepime$ or (cefiderocol$ or S-649266 or GSK-2696266) or cefoperazone$ or cefotaxime$ or ceftazidime$ or ceftibuten$ or ceftolozane$ or ceftriaxone$ or ciprofloxacin$ or colistin$ or colistimethate sodium or doripenem$ or (eravacycline$ or TP-434) or ertapenem$ or faropenem$ or fosfomycin$ or gentamicin$ or imipenem$ or levofloxacin$ or meropenem$ or minocycline$ or netilmicin$ or piperacillin$ or (plazomicin$ or ACHN-490) or polymixin$ or prulifloxacin$ or temocillin$ or ticarcillin$ or tobramycin$ or trimethoprim$ or (Relebactam$ or MK-7655)).tw. | 17452 |
| 3 | 1 and 2 | 2061 |
| 4 | limit 3 to english language [Limit not valid in CDSR; records were retained] | 1367 |
| 5 | limit 4 to yr="2017 -Current" | 136 |

**Table S3.** PICOTS eligibility criteria for the systematic literature review.

|  |  |
| --- | --- |
| Criterion | Description |
| Patient population | * Adults aged ≥18 years * Require hospitalization and treatment for cUTI caused by a bacterial infection |
| Interventions | * Imipenem/cilastatin/relebactam * Amikacin * Amoxicillin-clavulanic acid * Ampicillin-sulbactam * Aztreonam * Cefepime * Cefepime-tazobactam * Cefiderocol * Cefoperazone-sulbactam * Cefotaxime * Ceftazidime * Ceftazidime-avibactam * Ceftibuten * Ceftolozane-tazobactam * Ceftriaxone * Ciprofloxacin * Colistin * Doripenem * Eravacycline * Ertapenem * Faropenem * Fosfomycin * Gentamicin * Imipenem * Levofloxacin * Meropenem * Meropenem-sulbactam * Meropenem-vaborbactam * Minocycline * Netilmicin * Piperacillin-tazobactam * Plazomicin * Polymyxin * Prulifloxacin * Temocillin * Ticarcillin-clavulanic acid * Tobramycin * Trimethoprim-sulfamethoxazole |
| Comparators | Any intervention was accepted as a comparator |
| Outcomes | **Outcomes evaluated in feasibility assessment**   * Composite clinical and microbiological response at early follow-up * Microbiological response on therapy visit for each baseline pathogen (eradication, persistence, superinfection, indeterminate) * Microbiological response at end of therapy (sustained eradication, eradication, persistence, superinfection, indeterminate) * Microbiological response at early follow-up (sustained eradication, persistence, new infection, recurrence, indeterminate) * Clinical response on therapy visit (improved, persistence, progression, indeterminate) * Clinical response at end of therapy visit (cure, improved, failure, indeterminate) * Clinical response at early follow-up and post-randomization (sustained cure, cure, failure, relapse, indeterminate)   **Other outcomes**   * Serum creatinine level * Creatinine clearance * Hepatic function profile (total bilirubin, liver enzymes, and total protein tests) * Any AEs * Serious AEs * Treatment-related AEs (specifically nephrotoxicity, hepatotoxicity, and ototoxicity) |
| Timing | 2017-current |
| Study design | Phase 2/3 RCTs and controlled clinical trials (including blinded and open-label studies) |

AE, adverse event; cUTI, complicated urinary tract infection; PICOTS, population, intervention, comparator, outcome, time, and study design; RCT, randomized clinical trial.

**Table S4.** Risk of bias assessment using the Cochrane Collaboration Tool.[22]

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Random sequence generation** | **Allocation concealment** | **Blinding of participants and personnel** | **Blinding of outcome assessment** | **Incomplete outcome data** | **Selective reporting** | **Any other source of bias** |
| Wagenlehner, 2019 EPIC[38] | Low | Unclear | Low | Low | Low | Low | Low |
| Kaye, 2019 ZEUS[32] | Low | Unclear | Low | Low | Low | Low | Unclear |
| Wunderink, 2018 TANGO II[27] | Low | Unclear | High | Low | Low | Low | Low |
| Wagenlehner, 2018[37] | Unclear | Unclear | Low | Unclear | Low | Low | Low |
| RESTORE-IMI CSR, 2018[28] | Low | Low | Low | Low | Low | Unclear | Unclear |
| Portsmouth, 2018 APEKS-cUTI[34] | Low | Low | Low | Low | Low | Low | Low |
| Mir, 2018 PLEA[41] | Unclear | Unclear | Low | Unclear | Unclear | Unclear | Unclear |
| Kaye, 2018 TANGO I[31] | Low | Low | Low | Low | Low | Low | Low |
| Connolly, 2018[30] | Low | Low | Low | Low | Low | Low | Low |
| Chaudhary, 2018[25] | Unclear | Unclear | High | Unclear | Low | Unclear | Unclear |
| Sims, 2017[35] | Low | Low | Low | Low | Low | Low | Low |
| Wagenlehner, 2016 RECAPTURE 1 & 2[39] | Low | Low | Low | Unclear | Low | Low | Low |
| Carmeli, 2016  REPRISE[24] | Low | Low | High | High | Low | Low | Low |
| Wagenlehner, 2015 ASPECT-cUTI[40] | Low | Low | Low | Low | Low | Low | Low |
| Vazquez, 2012[36] | Low | Low | Low | Low | Low | Low | High |
| Sandberg, 2012[44] | Low | Low | Low | Low | Low | Low | Low |
| Naber, 2009 DORI-05[33] | Low | Low | Low | Low | Low | Low | Low |
| Peterson, 2008[42] | Low | Low | Low | Low | Unclear | Low | Low |
| Klausner, 2007[43] | Low | Low | Low | Low | Low | Low | Unclear |
| Carmignani, 2005[29] | Unclear | Unclear | Low | Low | Low | Low | Low |
| Naber, 2002[45] | Low | Low | Low | Low | Low | Low | Low |
| Hou, 2002[26] | Low | Low | High | High | Low | Low | Low |

**Table S5.** Patient baseline characteristics.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Treatment** | **Population** | **Age (years), mean (SD)** | **Sex, female, n (%)** | **Catheterization, n (%)a** |
| Wagenlehner, 2019 EPIC[38] | Plazomicin 15 mg/kg IV OD | mMITT: 191 | 58.8 (18.0) | 107 (56) | 13.1% of the patients had an indwelling urinary catheter |
| Meropenem 1000 mg IV q8h | mMITT: 197 | 60.0 (17.9) | 98 (49.7) |
| Kaye, 2019 ZEUS[32] | ZTI-01 6000 mg IV q8h | mMITT: 184 | 49.9 (20.92) | 119 (64.7) | NR |
| Piperacillin 4000 mg/ tazobactam 500 mg IV q8h | mMITT: 178 | 51.3 (20.71) | 111 (62.4) | NR |
| Wunderink, 2018 TANGO II[27] | Meropenem 2000 mg/ vaborbactam 2000 mg IV q8h | mCRE-MITT: 28 | 63.5 (14.1) | 18 (64.3) | 5 of the 7 cUTI patients had an indwelling urinary catheter at baseline |
| Best available therapy | mCRE-MITT: 15 | 60.2 (13) | 5 (33.3) |
| Wagenlehner, 2018[37] | Finafloxacin 800 mg IV/oral OD | ITT: 76  mITT: 64 | 54.6 (19.63) | 64 (84.2) | NR |
| Finafloxacin 800 mg IV/oral OD | ITT: 75  mITT: 68 | 58.0 (19.28) | 62 (82.7) | NR |
| Ciprofloxacin 400 mg or 500 mg oral BID | ITT: 72  mITT: 61 | 51 (21.01) | 57 (79.2) | NR |
| RESTORE-IMI CSR, 2018[28] | Imipenem-cilastatin 500 mg/relebactam 250 mg IV q6h | mMITT: 21  SmMITT: 28 | NR | mMITT: 8 (38.1)  SmMITT: 10 (35.7) | NR |
| Colistimethate sodium (colistin) loading dose 300 mg, maintenance 150 mg IV q12h, plus imipenem 500 mg IV q6h | mMITT: 13  SmMITT: 10 | NR | mMITT: 3 (30.0)  SmMITT: 3 (23.1) | NR |
| Portsmouth, 2018 APEKS-cUTI[34] | Cefiderocol 2000 mg IV q8h | ITT: 252 | 62.3 (16.10) | 133 (53) | Indwelling urinary catheter: 45 (18) |
| Imipenem 1000 mg/ cilastatin 1000 mg IV q8h | ITT: 119 | 61.3 (18.48) | 71 (60) | Indwelling urinary catheter: 17 (14) |
| Mir, 2018 PLEA[41] | Ceftriaxone 1000 mg/  sulbactam 500 mg/  EDTA 37 mg IV BID | mMITT: 74 | NR | NR | NR |
| Meropenem 1000 mg IV q8h | mMITT: 69 | NR | NR | NR |
| Kaye, 2018 TANGO I[31] | Meropenem 2000 mg/ vaborbactam 2000 mg IV q8h | mITT: 272 | 53.0 (19.4) | 181 (66.5) | NR |
| Piperacillin 4000 mg/ tazobactam 500 mg IV q8h | mITT: 273 | 52.6 (20.9) | 180 (65.9) | NR |
| Connolly, 2018[30] | Plazomicin 10 or 15 mg/kg IV OD | mITT: 12 | 41.5 (20.02) | 10 (83.3) | 1/8 (12.5) |
| Plazomicin 10 or 15 mg/kg IV OD | mITT: 51 | 39.5 (15.2) | 42 (82.4) | 4/27 (14.8) |
| Levofloxacin 750 mg IV OD | mITT: 29 | 47.9 (15.1) | 25 (86.2) | 1/12 (8.3) |
| Chaudhary, 2018[25] | Ceftriaxone/ sulbactam/disodium EDTA 3000 mg IV OD | Randomized: 102 | 35 (13.96) | 42 (41.2) | NR |
| Ceftriaxone 2000 mg IV OD | Randomized: 102 | 40 (14.26)) | 46 (45.1) | NR |
| Sims, 2017[35] | Imipenem 500 mg/ cilastatin 500 mg/ relebactam 250 mg IV q6h | ME: 71 | 58 (Range: 18-90) | 38 (53.5) | Indwelling catheterization including Foley and others: 1 (1.4) |
| Imipenem 500 mg/ cilastatin 500 mg/ relebactam 125 mg IV q6h | ME: 79 | 60 (Range: 19-84) | 45 (57.0) | Indwelling catheterization including Foley and others: 2 (2.53) |
| Imipenem 500 mg/ cilastatin 500 mg + placebo IV q6h | ME: 80 | 61 (Range: 18-86) | 36 (45.0) | Indwelling catheterization including Foley and others: 4 (5) |
| Wagenlehner, 2016 RECAPTURE 1 & 2[39] | Ceftazidime 2000 mg/ avibactam 500 mg IVq8h | mMITT: 393 | 51.4 (20.2) | 272 (69.2) | NR |
| Doripenem 500 mg IV q8h | mMITT: 417 | 53.3 (18.6) | 293 (70.3) | NR |
| Carmeli, 2016 REPRISE[24] | Ceftazidime 2000 mg/  avibactam 500 mg q8h | ITT: 144 | 64.3 (14.6) | 64 (44) | NR |
| Best available therapy | ITT: 137 | 61.3 (15.3) | 63 (46) | NR |
| Wagenlehner, 2015 ASPECT-cUTI[40] | Ceftolozane/tazobactam 1500 mg IV q8h | ITT: 543  MITT: 534  mMITT: 398 | 49.1 (197) | 293 (73.6) | Urinary catheter  11 (2.8) |
| Levofloxacin 750 mg IV OD | ITT: 540  MITT: 534  mMITT: 402 | 48.1 (20.2) | 299 (74.4) | Urinary catheter  10 (2.5) |
| Vazquez, 2012[36] | Ceftazidime 500 mg/ avibactam 125 mg IV q8h | Safety: 68  ME: 27 | 46.4 (18.2) | 51 (75.0) | NR |
| Imipenem-cilastatin 500 mg IV q6h | Safety: 67  ME: 35 | 48.2 (18.4) | 49 (73.1) | NR |
| Sandberg, 2012[44] | Ciprofloxacin 500 mg oral BID | PP: 73 | 46 (IQR: 27-62) | 73 (100) | NR |
| Ciprofloxacin 500 mg oral BID | PP: 83 | 41 (IQR: 23- 58) | 83 (100) | NR |
| Naber, 2009 DORI-05[33] | Doripenem 500 mg IV q8h | Randomized: 377  mMITT: 327 | 51.2 (21.1) | 234 (62.1) | 56 (14.9) |
| Levofloxacin 250 mg IV q8h | Randomized: 376  mMITT: 321 | 51.1 (21.0) | 230 (61.2) | 72 (19.1) |
| Peterson, 2008[42] | Levofloxacin 750 mg IV or oral OD | ITT: 537 | NR | 330 (61.5) | n=67 |
| Ciprofloxacin 400 mg IV or 500 mg oral BD | ITT: 556 | NR | 336 (60.4) |
| Klausner, 2007[43] | Levofloxacin 750 mg IV or oral OD | ITT: 146 | 38.9 (17.96) | 138 (94.5) | NR |
| Ciprofloxacin 400 mg IV or 500 mg oral BD | ITT: 165 | 39.4 (17.05) | 161 (97.6) | NR |
| Carmignani, 2005[29] | Prulifloxacin 600 mg oral OD | Randomized: 127 | 62.29 (17.11) | 92 (72) | NR |
| Ciprofloxacin 500 mg oral BID | Randomized: 130 | 62.35 (15.98) | 91 (70) | NR |
| Naber, 2002[45] | Piperacillin 4000 mg/ tazobactam 500 mg IV q8h | Randomized: 166 | 59.1 (17.5) | 68 (41.0) | 69 (47.9) |
| Imipenem 500 mg/ cilastatin 500 mg IV q8h | Randomized: 171 | 58.7 (18.7) | 76 (44.4) | 68 (44.4) |
| Hou, 2002[26] | Meropenem 500 mg or 100 mg IV BID | Randomized: 70 | 48.7 (15.7) | 41 (58.6) | NR |
| Imipenem 500 mg or 1000 mg/cilastatin 500 mg or 1000 mg IV BID | Randomized: 70 | 48.2 (16.4) | 31 (45.7) | NR |

aUnless otherwise indicated.

BID, twice daily; IQR, interquartile range; ITT, intention to treat; IV, intravenously; mCREMITT, microbiologic carbapenem-resistant Enterobacteriaceae modified intent to treat; ME, microbiologically evaluable; mg, milligram; MITT, modified intent to treat; mMITT, microbiological modified intent to treat; NR, not reported; OD, once daily; PP, per protocol; q6h; once every 6 hours; q8h, once every 8 hours; SmMiTT, supplemental microbiological modified intent to treat.

**Figure S1.** PRISMA flow diagram.

**Diagram

Description automatically generated**

CSR, clinical study report; NMA, network meta-analysis; SLR, systematic literature review.