Clinical Practice Guideline by Infectious Diseases Society of America (IDSA): 2025 Guideline on Management and Treatment of Complicated Urinary Tract Infections

Supplementary material for Selection of Antibiotic Therapy for Complicated UTI

A. Initial Selection among Empiric Antibiotic Options for cUTI

Empiric Treatment of complicated UTI by Specific Antibiotic Classes

For all antibiotic classes except older aminoglycosides

Methods

-Literature Search Strategies

-Eligibility criteria for selection of the studies

Tables and Figures

-Supplementary Figure A.1: PRISMA flow diagram of study identification and selection

-Supplementary Table A.1: Characteristics of included studies

-Supplementary Figure A.2: Summary of the Risk of Bias of included studies

-Supplementary Table A.2: Assessment of the Risk of Bias of the included studied

-GRADE Evidence Profile and Forest plots for each patient-important outcome

1) **Ceftriaxone / third and fourth generation cephalosporins** (Supplementary Table and Figures A.3)
2) **Piperacillin-tazobactam** (Supplementary Table and Figures A.4)
3) **Fluoroquinolones** (Supplementary Table and Figures A.5)
4) **Carbapenems (without BLI)** (Supplementary Table and Figures A.6)
5) **Novel beta-lactam/beta-lactamase inhibitors (BLBLI)** (Supplementary Table and Figures A.7)
6) **Cefiderocol** (Supplementary Table and Figures A.8)
7) **Plazomicin** (Supplementary Table and Figures A.9)
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For older aminoglycosides

Methods

-Literature Search Strategies

-Eligibility criteria for selection of the studies

Tables and Figures

-Supplementary Figure A.11: PRISMA flow diagram of study identification and selection

-Supplementary Table A.11: Characteristics of included studies

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-Supplementary Table A.13: GRADE Evidence Profile
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B. Stepwise Process to Guide Empiric Antibiotic Choice for cUTI

-Step 1: Severity of illness: Impact of Inappropriate Empiric Antibiotic Therapy (IEAT)

Methods

-Literature Search Strategies
-Eligibility criteria for selection of the studies

Tables and Figures (section B1)

-Supplementary Figure B1.a: PRISMA flow diagram of study identification and selection
-Supplementary Table B1.a: Characteristics of included studies for the impact of IEAT on mortality
-Supplementary Table B1.b: Summary of the Risk of Bias of included studies
-Supplementary Table B1.c: GRADE Evidence Profile
-Supplementary Figures B1.b: Forest plots for mortality

-Step 2: Patient-specific risk factors for resistant uropathogens

Methods

General concepts (section 2)
Literature Search Strategies

Table and Figures (section B2)

-Supplementary Figures B2: PRISMA flow diagrams of study identification and selection

a) Improvement of appropriateness of EAT
b) Risk factors for resistant uropathogens

2A) Prior urine cultures (section B2A)

-Supplementary Table B2A.1: Characteristics of the included studies
-Supplementary Table B2A.2: Assessment of the Risk of Bias of the included studies
-Supplementary Figures B2A.1: Forest plot for appropriateness of empiric antimicrobial therapy
-Supplementary Table B2A.3: Certainty of evidence for the impact of prior urine cultures on appropriateness of empiric antimicrobial therapy

Supporting evidence

<u>-Predictive value of prior urine culture (paired urine cultures)</u>

-Methods (specific to the subsection)
-Supplementary Table B2A.4: Characteristics of the included studies
-Supplementary Table B2A.5: Estimating predictive values of prior urine cultures for current uropathogen susceptibility (NPV) or resistance (PPV)

-Prior urine culture as a risk factor

-Methods (specific to the subsection)

-Supplementary Table B2A.6: Characteristics of included the studies

2B) Risk factors of resistance to a specific antibiotic class (section B2B)

-Methods (specific to section B2B)

- Risk factors of resistance

-Supplementary Table B2B.1: Characteristics of the included studies

-Supplementary Table B2B.2: Assessment of the Risk of Bias of the included studies

-Supplementary Figure B2B.1: Forest plot for the impact of time interval between prior FQ exposure on FQ resistance

-Supplementary Table B2B.3: Certainty of the evidence for the impact of prior FQ exposure on FQ resistance

-Step 4: Antibiogram (for septic patients due to cUTI)

-Modeling to establish antibiogram threshold based on excess mortality

-Supplementary Table B4.1: Modeling in patients with cUTI and associated septic shock in ICU

-Supplementary Table B4.2: Modeling in patients with cUTI and associated sepsis without shock

-Supplementary Table B4.3: Modeling in patients with cUTI without associated sepsis

-Supplementary Figure B4.1: Forest plot for clinical failure

Supplementary Table: GRADE Evidence to Decision framework (general concepts used for the decision-making process)

A. Empiric Treatment of complicated UTI by Specific Antibiotic Classes

For all antibiotics classes except older aminoglycosides

Literature Search Strategy (last updated September 15th, 2024)

Medline (PubMed)

1. cystitis OR cystitis[MeSH Terms]
2. pyelonephritis OR pyelonephritis[MeSH Terms]
3. (complicat* AND ("urinary tract infection" OR "urinary tract infections") OR urinary tract infection[MeSH Terms])
4. #1 OR #2 OR #3
5. fosfomycin
6. fluoroquinolones
7. amox-clav
8. cephalosporins
9. pivmecillinam
10. ciprofloxacin
11. levofloxacin
12. cephalexin
13. cefaclor
14. cefadroxil
15. cefpodoxime
16. cefdinir
17. cefixime
18. trimethoprim
19. sulfamethoxazole
20. (extended spectrum penicillins)
21. delafloxacin
22. cefazolin
23. cefotetan
24. cefoxitin
25. cefuroxime
26. ceftriaxone
27. ceftazidime
28. cefotaxime
29. cefepime
30. ampicillin-sulbactam
31. piperacillin-tazobactam
32. carbapenems
33. imipenem-cilastatin
34. meropenem
35. doripenem
36. ertapenem
37. aminoglycosides
38. gentamicin
39. amikacin
40. tobramycin
41. ceftolozane-tazobactam
42. ceftazidime-avibactam
43. meropenem-vaborbactam
44. imipenem-relebactam
45. plazomicin
46. cefiderocol
47. tebipenem

48. eravacycline
49. omadacycline
50. "omadacycline" [Supplementary Concept]
51. "polymyxin B"[Mesh]
52. “polymyxin b”
53. colistin[Mesh]
54. colistin
55. “polymyxin e”
56. "gepotidacin" [Supplementary Concept]
57. gepotidacin
58. #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57
59. #4 AND #48
60. “randomized controlled trial” OR “clinical trial” OR "randomized controlled trial"[Publication Type] OR "clinical trial"[Publication Type] OR "clinical trial, phase i"[Publication Type] OR "clinical trial, phase ii"[Publication Type] OR "clinical trial, phase iii"[Publication Type] OR "clinical trial, phase iv"[Publication Type]
61. #59 AND #60
62. "2008"[Date - Publication] : "3000"[Date - Publication]
63. #61 AND #62
64. "english"[Language]
65. #63 AND #64

Run: 10.18.20 / Updated: 2.15.23, 9.1.23 and 9.15.24

Embase

1. ('urinary tract infection' OR 'urinary tract infections') AND complicat*
2. cystitis OR pyelonephritis
3. 'urinary tract infection'/exp OR 'cystitis'/exp OR 'pyelonephritis'/exp
4. #1 OR #2 OR #3
5. 'fosfomycin'/exp OR fosfomycin
6. 'quinolone derivative'/exp
7. fluoroquinolones
8. 'amox clav'
9. 'cephalosporin derivative'/exp
10. cephalosporins
11. 'pivmecillinam'/exp OR pivmecillinam
12. 'ciprofloxacin'/exp OR ciprofloxacin
13. 'levofloxacin'/exp OR levofloxacin
14. 'cefalexin'/exp OR cephalexin
15. 'cefaclor'/exp OR cefaclor
16. 'cefadroxil'/exp OR cefadroxil
17. 'cefpodoxime'/exp OR cefpodoxime
18. 'cefdinir'/exp OR cefdinir
19. 'cefixime'/exp OR cefixime
20. 'trimethoprim'/exp OR trimethoprim
21. 'sulfamethoxazole'/exp OR sulfamethoxazole
22. 'extended spectrum penicillins'
23. 'delafloxacin'/exp OR delafloxacin
24. 'cefazolin'/exp OR cefazolin
25. 'cefotetan'/exp OR cefotetan
26. 'cefoxitin'/exp OR cefoxitin
27. 'cefuroxime'/exp OR cefuroxime
28. 'ceftriaxone'/exp OR ceftriaxone
29. 'ceftazidime'/exp OR ceftazidime
30. 'cefotaxime'/exp OR cefotaxime

31. 'cefepime'/exp OR cefepime
32. 'sultamicillin'/exp
33. 'ampicillin sulbactam'
34. 'piperacillin plus tazobactam'/exp OR 'piperacillin tazobactam'
35. 'carbapenem derivative'/exp
36. carbapenems
37. 'cilastatin plus imipenem'/exp OR 'imipenem cilastatin'
38. 'meropenem'/exp OR meropenem
39. 'doripenem'/exp OR doripenem
40. 'ertapenem'/exp OR ertapenem
41. 'aminoglycoside'/exp OR aminoglycosides
42. 'gentamicin'/exp OR gentamicin
43. 'amikacin'/exp OR amikacin
44. 'tobramycin'/exp OR tobramycin
45. 'ceftolozane plus tazobactam'/exp OR 'ceftolozane tazobactam'
46. 'avibactam plus ceftazidime'/exp OR 'ceftazidime avibactam'
47. 'meropenem plus vaborbactam'/exp OR 'meropenem vaborbactam'
48. 'imipenem relebactam'
49. 'plazomicin'/exp OR plazomicin
50. 'cefiderocol'/exp OR cefiderocol
51. 'tebipenem'/exp OR tebipenem
52. 'eravacycline'/exp OR eravacycline
53. 'omadacycline'/exp OR omadacycline
54. 'polymyxin b'/exp OR 'polymyxin b'
55. 'polymyxin e'
56. gepotidacin'/exp
57. 'colistin'/exp
58. 'omadacycline'/exp OR omadacycline
59. #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58
60. #4 AND #59
61. clinical trial'/de OR 'controlled clinical trial'/de OR 'phase 3 clinical trial'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial' OR 'clinical trial'
62. #60 AND #61
63. english:la
64. #62 AND #63
65. [01-01-2008]/sd NOT [16-09-2024]/sd
66. #64 AND #65

Run: 10.16.20 / Update: 2.15.23, 9.1.23 and 9.15.24

Cochrane

1. MeSH descriptor: [Cystitis] explode all trees
2. MeSH descriptor: [Pyelonephritis] explode all trees
3. MeSH descriptor: [Urinary Tract Infections] explode all trees
4. cystitis
5. pyelonephritis
6. complicat* AND ("urinary tract infection" OR "urinary tract infections")
7. #1 OR #2 OR #3 OR #4 OR #5 OR #6
8. fosfomycin
9. fluoroquinolones
10. amox-clav
11. cephalosporins
12. pivmecillinam
13. ciprofloxacin

14. levofloxacin
15. cephalexin
16. cefaclor
17. cefadroxil
18. cefpodoxime
19. cefdinir
20. cefixime
21. trimethoprim
22. sulfamethoxazole
23. (extended spectrum penicillins)
24. delafloxacin
25. cefazolin
26. cefotetan
27. cefoxitin
28. cefuroxime
29. ceftriaxone
30. ceftazidime
31. cefotaxime
32. cefepime
33. ampicillin-sulbactam
34. piperacillin-tazobactam
35. carbapenems
36. imipenem-cilastatin
37. meropenem
38. doripenem
39. ertapenem
40. aminoglycosides
41. gentamicin
42. amikacin
43. tobramycin
44. ceftolozane-tazobactam
45. ceftazidime-avibactam
46. meropenem-vaborbactam
47. imipenem-relebactam
48. plazomicin
49. cefiderocol
50. tebipenem
51. eravacycline
52. omadacycline
53. 'polymyxin b'
54 'polymyxin e'
55. gepotidacin
56. colistin
57. omadacycline
58. #8 OR #9 OR # 10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57
59. #7 AND #58

Run: 10.18.20 / Updated: 2.15.23, 9.1.23 and Updated: 9.15.24

Eligibility criteria for selection of the studies

Inclusion criteria:

- Patient population: Adults patients presenting cUTI (with or without sepsis, with or without risk of resistance)
- Intervention / Comparators: any direct comparison between antibiotics of interest from the following list (either parenteral or oral):
  - -Cephalosporins:
    - Oral: First generation cephalosporins: cephalexin; Second generation cephalosporins: cefuroxime axetil, cefaclor, cefadroxil; Third generation cephalosporins: cefpodoxime, cefdinir, cefixime
    - Parenteral: First generation cephalosporins: cefazolin; Second generation cephalosporins: Cefotetan, Cefoxitin, Cefuroxime; Third generation cephalosporins: ceftriaxone, ceftazidime, cefotaxime; Fourth generation cephalosporins: cefepime
  - -Extended spectrum penicillins:
    - Oral: amoxicillin-clavulanate, pivmecillinam
    - Parenteral: ampicillin-sulbactam, piperacillin-tazobactam
  - -Fluoroquinolones (oral or parenteral): ciprofloxacin, levofloxacin, delafloxacin
  - -Trimethoprim/sulfamethoxazole and trimethoprim
  - -Carbapenems (parenteral): imipenem-cilastatin, meropenem, doripenem, ertapenem
  - -Novel beta-lactam/beta-lactam inhibitors (BLBLI) with cUTI approval: ceftolozane-tazobactam, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, cefepime-enmetazobactam
  - -Cefiderocol (parenteral)
  - -Plazomicin (parenteral)
  - -Fosfomycin (Intravenous or intramuscular)
  - -Older aminoglycosides (parenteral): gentamicin, amikacin, tobramycin
  - -Polymyxins (parenteral): polymyxin B and polymyxin E (colistin)
- -Outcomes
  - -Minimally including clinical cure (at TOC)
- Study design: Randomized controlled trials (RCTs)
- Year: published from 2008 up to present
- Language: English only

Exclusion criteria:

- -Patient population:
  - -Children
  - -Renal transplant patients
  - -Neutropenic patients
  - -Pregnant women and lactating women
  - -Uncomplicated UTI
- -Intervention / Comparator
  - -Any comparison not including antibiotics from the list above for BOTH the intervention AND the comparator of interest
  - -Any comparison within the same class of antibiotics (e.g. levofloxacin vs ciprofloxacin)
  - -Any comparison of different doses of the same antibiotic (e.g. ciprofloxacin XR 100mg die vs 500mg BID)
  - -Any comparison including antibiotics not available in US (e.g. cefoselis, sitafloxacin, plurifloxacin, finafloxacin, biapenem, temocillin)

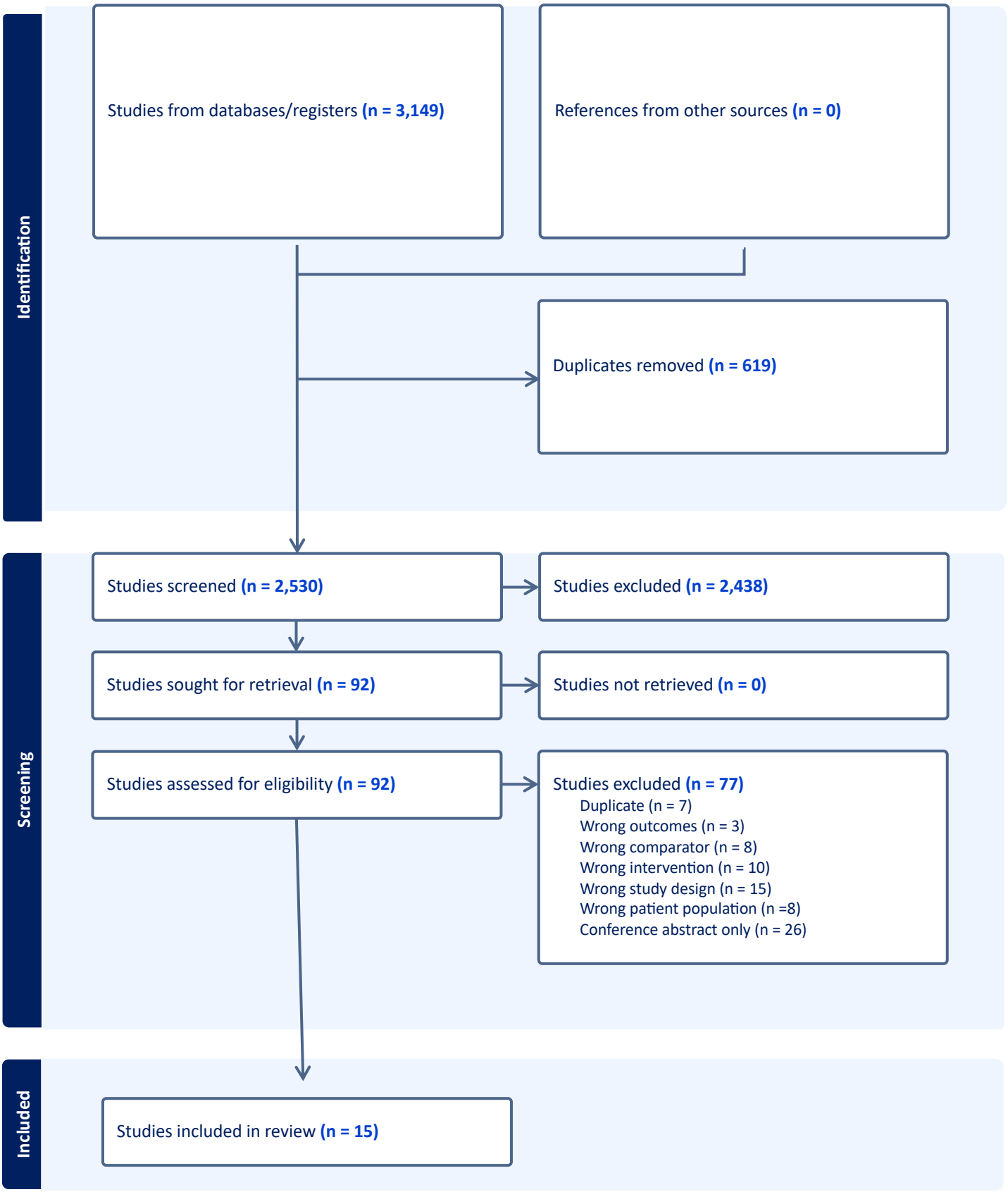
-Any comparison including BLBLI not yet approved for cUTI (e.g. ceftriaxone-sulbactam-EDTA, cefipime-taniborbactam)

-Any comparison including an antibiotic from the list above but only as part of a combination therapy

-Outcome

-Not including clinical cure (at TOC) (e.g. measuring clinical cure at 72 hours after initiation of antibiotics, which was not judged meaningful by the panel)

Supplementary Figure A.1: Prisma Flow Diagram of study identification and selection (last updated September 15th, 2024)



Supplementary Table A.1: Characteristic of the included studies (n=15, 2008-2024)

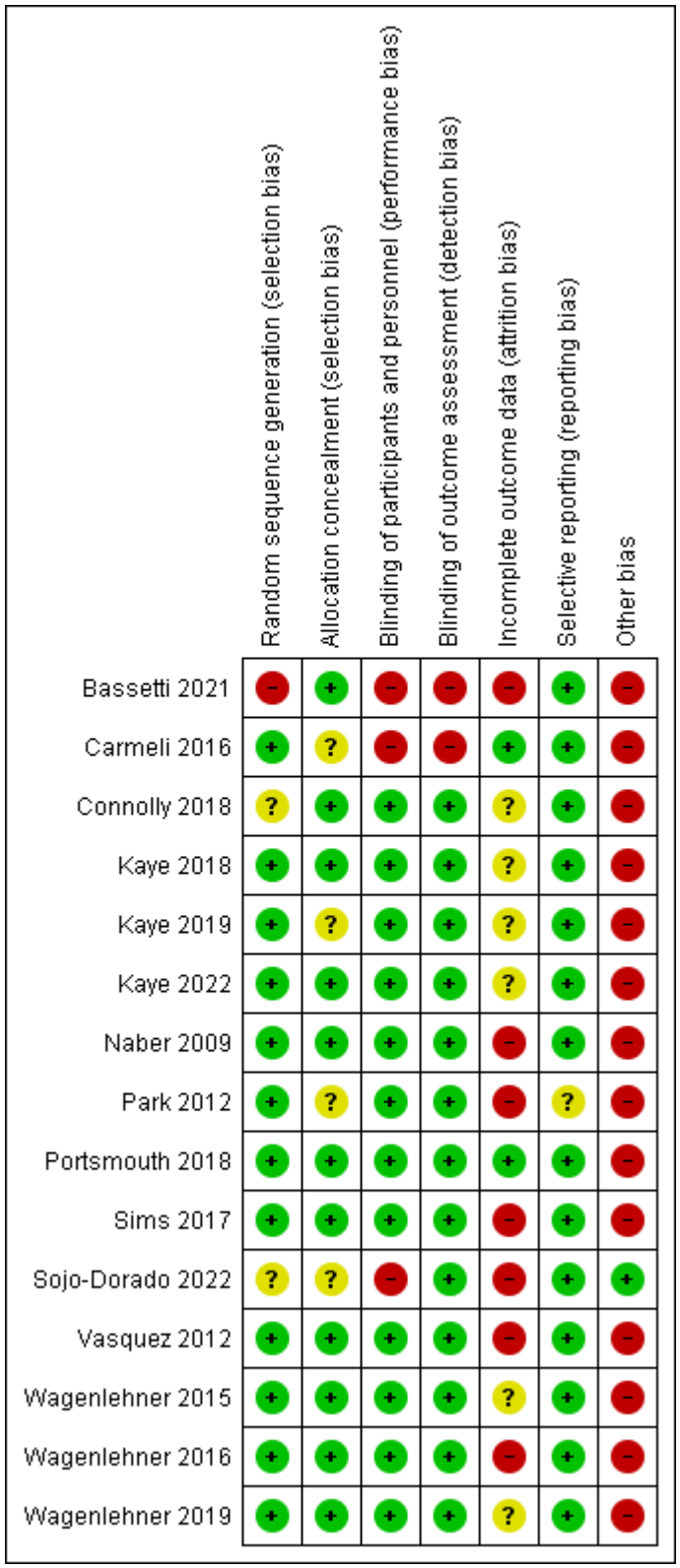
Study *(Lead author, Year of publication, Name of trial, Countries)*	**Population** *(Type UTI, Year of enrollment, n randomised, F (%), Age)*	**Study design** *(Non-inferiority margin if applicable, primary outcome with its timing)*	**Main uro-pathogens**	**Intervention** *(Antibiotic(s), % of resistance)*	**Comparator** *(Antibiotic(s), % of resistance)*	**Duration and Route of administration**
Kaye 2022 ALLIUM 19 countries	cUTI/AP, only uropathogens S to both studied drugs 2018-2019 N=1041 F: 54.9% Age: 55y	Phae 3 Non-inferiority trial Margin of 10% CC/ MC at day 14 = at TOC (7 +/- 2 days after end of treatment)	*E. coli* (76%) and *K. pneumoniae* (10%)	Cefepime - enmetazobactam R: 0%, since exclusion criteria	Piperacillin - tazobactam R: 0%, since exclusion criteria	IV: 7 days PO: no transition to oral Total duration: 8 days
Sojo-Dorado 2022 FOREST Spain (multicentric)	cUTI/AP, only patient with MDR *E. coli* bacteremia 2014-2018 N=161 F: 51.0% Age: 72y	Non-inferiority trial Margin of 7% for CC/MC at TOC (5 to 7 days after end of treatment)	MDR *E. coli* (100%)	IV Fosfomycin R: 0%, since exclusion criteria	Ceftriaxone OR meropenem if ceftriaxone-R Meropenem-R: 0%, since exclusion criteria (but ceftriaxone-R: 45.2% (33/73)) the comparator group	IV: received for 5 to 6 days PO (allowed after 4 days of IV): oral fosfomycin (85% of fosfomycin group) vs cefuroxime axetil, ciprofloxacin, amoxicillin-clavulanate, or TMP/SMX in the comparator group Total duration: 10 to 14 days
Bassetti 2021 CREDIBLE-CR International	cUTI, only GN Carba-R 2016- 2019 N=152 various types of infections (but n=36 for the subset with cUTI) F: 32.6% Age: 63y	Descriptive study MC at TOC (5 to 9 days after the end of treatment)	*K. pneumoniae* (64%) and *P. aeruginosa* (26%)	Cefiderocol Not reported for cUTI group	Best Available Therapy (mostly colistin based regimen) Not reported for cUTI group	IV: received for 11 days in the Cefiderocol group vs 7 days in the BAT group PO: no transition to oral (NR) Total duration: 7 to 14 days
Kaye 2019 ZEUS 16 countries	cUTI/AP, empiric Tx 2016-2017 N=465 F: 63.4% A: 51y	Phase 2/3 Non-inferiority trial Margin of 15% for CC/MC at TOC (day 19 to 21)	*E. coli* (72%) and *K. pneumoniae* (15%)	IV Fosfomycin R: 0% in *E. coli*	Piperacillin-tazobactam R: 10.2% (17/167) the piperacillin-tazobactam group of the mMITT	IV: 7 days PO: no transition to oral Total duration: 7 (up to 14 days if concurrent bacteremia)
Wagenlehner 2019 EPIC North America and Europe	cUTI/AP, only uropathogens S to both studied drugs 2016 N=609 F: 52.8% A: 57y	Non-inferiority trial Margin of 15% for CC/MC at day 5 and TOC (day 15 to 19)	*E. coli* (67%) and *K. pneumoniae* (19%)	Plazomicin R: 0%, since exclusion criteria	Meropenem R: 0%, since exclusion criteria	IV: received for 5 days PO (allowed after 4 days of IV): transition to oral levofloxacin (or alternative such as TMP/SMX, amoxicillin-clavulanate and cefixime) for another 4 days Total duration: 7 to 10 days
Portsmouth 2018 APEKS 15 countries	cUTI/AP, empiric Tx 2015-2016 N=452	Phase II, Non-inferiority trial Margin of 15% for CC/MC at TOC (5 to 9	*E. coli* (62%) and *K. pneumoniae* (20%)	Cefiderocol R: 0%	Imipenem-cilastatin R: 3.8% (4/105) the Imipenem group of the mMITT	IV: received for 9 days PO: no transition to oral Total duration: 7 to 14 days

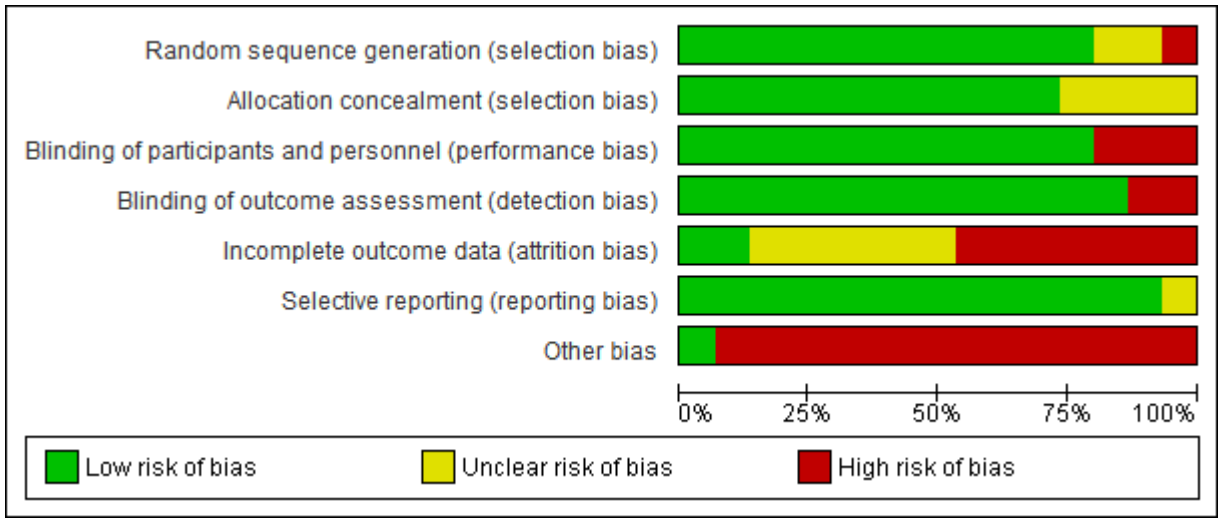
	F: 55.0% Age: 62y	days after end of treatment)				
Kaye 2018 TANGO I 17 countries	cUTI/AP, empiric Tx 2014-2016 N=550 F: 66.2% Age: 53y	Non-inferiority trial Margin of 15% CC/ MC at the end of IV treatment and MC at TOC (5 to 9 days after end of treatment)	*E. coli* (65%) and *K. pneumoniae* (16%)	Meropenem-vaborbactam Not reported for meropenem-vaborbactam, but Meropenem-R: 0.7% (1/154) in the meropenem-vaborbactam group of the mMITT	Piperacillin-tazobactam R: 10.6% (15/142) in the piperacillin-tazobactam group of mMITT	IV: received for 8 days PO: transition to oral levofloxacin for another 2 days Total duration: 10 days
Connolly 2018 US, India, Columbia and Chile	cUTI/AP, empiric Tx 2010-2012 N=145 F: 83.7% Age: 42y	Phase II, Descriptive study MC at TOC (5 to 12 days after end of treatment)	*E. coli* (71%) and *K. pneumoniae* (6%)	Plazomicin R: 7.1% (3/42) in the 2 plazomicin groups of the ME	Levofloxacin R: 14.3% (3/21) in the levofloxacin group of the ME	IV: 5 days PO: no transition to oral Total duration: 5 days
Sims 2017 11 countries	cUTI/AP, empiric Tx 2012-2015 N=132 F: 51.7% Age: 59y	Phase II, Non-inferiority trial with nested superiority phase 2b dose-ranging study Margin of 15% for MC at end of IV treatment	*E. coli* (62%) and *K. pneumoniae* (15%)	Imipenem-cilastatin-relabactam R: 6.8% (15/220) in the MITT	Imipenem-cilastatin R: 11.4% (25/220) in the MITT	IV: received for 7 to 8 days PO (allowed 5 days of IV): transition to oral ciprofloxacin Total duration: 5 to 14 days
Carmeli 2016 REPRISE 16 countries	cUTI, only ceftazidime-R Enterobacteriaceae and *P. aeruginosa* 2013-2014 N=333 with either cUTI or cIAI (of which 306 cUTI) F: 45.4% Age: 62y	Descriptive trial CC at TOC (7 to 10 days after end of treatment)	*E. coli* (42%) and *K. pneumoniae* (42%)	Ceftazidime-avibactam R: 1.5% (2/132) in the ceftazidime-avibactam group of the mMITT	Best available therapy (of which 97% carbapenems: meropenem and imipenem) R: 5.1% (7/137) in the BAT group of the mMITT	IV: received 10 days PO: no transition to oral Total duration: ranging from 2 to 21 days
Wagenlehner 2016 RECAPTURE 1 and 2 25 countries	cUTI/AP, empiric Tx 2012-2014 N=1033 F: 69.8% Age: 52y	Non-inferiority trial Margin of 10% for CC at day 5 and, CC/MC at TOC, and 12.5% for MC TOC (day 21 to 25)	*E. coli* (74%) and *K. pneumoniae* (12%)	Ceftazidime-avibactam R: 0.2% (2/803) in the mMITT	Doripenem R: 3.0% (4/803) in the mMITT	IV: 7 to 8 days PO (allowed after 5 days of IV): transition to oral ciprofloxacin or TMP/SMX Total duration: 5 to 10 days (up to 14 days of bacteremic)
Wagenlehner 2015 ASPECT-cUTI International	cUTI/AP, empiric Tx 2011-2013 N=1083 F: 74.0% Age: 49y	Phase 3, Non-inferiority trial Margin of 10% for CC/MC (5 to 9 days after end of treatment)	*E. coli* (79%) and *K. pneumoniae* (7%)	Ceftolozane-Tazobactam R: 2.7% (20/731) in the mMITT	Levofloxacin (change of drug was allowed if FQ-resistant) R: 26.7% (195/731) in the mMITT	IV: 7 days PO: no transition to oral Total duration: 7 days
Vasquez 2012 US, India, Jordan, Lebanon and Guatemala	cUTI, only GN uropathogens S to both studied drugs 2008-2010	Phase 2, Descriptive MC at TOC (5 to 9 days after end of treatment)	*E. coli* (94%)	Ceftazidime-avibactam R: 0%, since exclusion criteria	Imipenem-cilastatin R: 0%, since exclusion criteria	IV: received for 5 to 6 days PO (allowed after 4 days of IV): transition to oral

	N=137 F: 74.1% Age: 47y					ciprofloxacin (or alternative if R) for another 5 to 6 days Total duration: 7 to 14 days
Park 2012 South Korea (multicentric)	cUTI/AP, empiric Tx 2008-2009 N=271 F: 90.4% Age: 58y	Non-inferiority trial Margin 20% for CC/MC at TOC (5 to 9 days after end of treatment)	*E. coli* (85%) and *K. pneumoniae* (5%)	Ertapenem R: 0% in the MITT, since exclusion criteria	Ceftriaxone R: 0% in the MITT, since exclusion criteria	IV: received 5 days PO (allowed after 3 days of IV): transition to oral ciprofloxacin or cefixime for another 5 days Total duration: 7 to 14 days
Naber 2009 International	cUTI/AP, empiric Tx 2003-2006 N=753 F: 61.6% Age: 51y	Non-inferiority trial Margin of 10% for MC at TOC (5 to 9 days after end of treatment)	*E. coli* (74%), *P. mirabilis* (7%) and *K. pneumoniae* (5%)	Doripenem R: 0.5% (3/648) in the mMITT	Levofloxacin R: 14.8% (96/648) in the mMITT	IV: received for 5 days PO: transition to oral levofloxacin for 6 days Total duration: 9 to 10 days

UTI: urinary tract infection; cUTI: complicated UTI; uUTI: uncomplicated UTI; AP: acute pyelonephritis; cIAI: complicated intraabdominal infection; N: number; F: female, y: years; NR: not reported; Tx: therapy
R: resistant, including non-susceptible; S: susceptible; MDR: multidrug resistant
CC: clinical cure or response; MC: microbiologic cure, eradication, or response; TOC: test of cure; IV: parenteral
MITT: modified intent-to-treat; mMITT: microbiological modified intent-to-treat; ME: microbiologically evaluable; BAT: best available therapy; TMP/SMX: trimethoprim/sulfamethoxazole

Supplementary Figure A.2: Summary of the Risk of Bias of included studies (Cochrane Risk of Bias tool) (n 15)




Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias

Supplementary Table A.2: Assessment of the Risk of Bias of included studies (Cochrane Risk of bias Tool) (n=15)

Study *(Lead author, Year of publication, Name of trial, Countries)*	**Random sequence generation** (selection bias)	**Allocation concealment** (selection bias)	**Blinding of participants and personnel** (performance bias)	**Blinding of outcome assessment** (detection bias)	**Incomplete outcome data** (attrition bias) *	**Selective reporting** (reporting bias)	**Other bias** (e.g. sources of funding)
Bassetti 2021 CREDIBLE-CR	High RoB -Randomization 2:1 (not further detailed) -Comparable patients' characteristics at baseline (ITT), but comparison very likely underpowered -Only a very small subpopulation was diagnosed with cUTI	Low RoB -Interactive web/ voice response system	High RoB -Open-label (especially applicable to subjective outcomes)	High RoB -Open-label (especially applicable to subjective outcomes)	High RoB -Early withdrawal after randomisation (mITT = who had a carbapenem-resistant Gram-negative pathogen isolated from appropriate specimen and received at least one dose of the study drug) resulted in an attrition that was relatively frequent and asymmetrical between groups (21% vs 26%).	Low RoB	High RoB -Industry-funded: the sponsor of the study (related to one of the studied molecules) provided the enrolling sites, and had a role in study design, protocol development, writing the statistical analysis plan, data collection, data analysis, data interpretation, and writing of the report. The authors, which included employees and/or consultants of the same company, had final responsibility for the decision to submit for publication.
Carmeli 2016 REPRISE	Low RoB -Computer-generated randomization -Comparable patients' characteristics at baseline (mMITT)	Unclear RoB -Computer generated randomization scheme provided by the sponsor (not detailed)	High RoB -Open-label (especially applicable to subjective outcomes)	High RoB -Open-label (especially applicable to subjective outcomes)	Low RoB -Early withdrawal after randomisation (mMITT = who met the diagnosis of cUTI, had at least one ceftazidime-resistant Gram-negative pathogen, and received at least one dose of the study drug) resulted in an attrition that was infrequent and symmetrical between groups (6% vs 10%).	Low RoB	High RoB -Industry-funded: the sponsor of the study (related to one of the studied molecules) was responsible for study design and data collection, and with the authors employed or contracted by the funder were responsible for data interpretation and writing of this report. The authors, which included employees and consultant of the same company, had final responsibility for the decision to submit for publication.
Connolly 2018	Unclear RoB -Randomization initially 1:1:1 then 2:1 (enrollment in the low dose treatment group was stopped during the study to allow preferential enrollment in the higher-dose group) -Comparable patients' characteristics at baseline (MITT)	Low RoB -Central interactive voice response system	Low RoB -Double-blinded	Low RoB -Double-blinded	Unclear RoB -Early withdrawal after randomisation (MITT = who had at least one isolated causative bacterial pathogen in a pretreatment urine specimen) resulted in an attrition that was frequent and symmetrical between groups (36% vs 38%).	Low RoB	High RoB -Partially funded by industry: Involvement of industry not reported (the sponsor was related to one of the studied molecules) but the authors, which included employees, contractors and/or stakeholders of the same company.
Kaye 2018 TANGO I	Low RoB -Computer-generated central randomization, using a dynamic randomization algorithm -Comparable patients'	Low RoB -Interactive web/ voice response system	Low RoB -Double-blinded	Low RoB -Double-blinded	Unclear RoB -Early withdrawal after randomisation (mMITT = who had at least one isolated bacterial pathogen in urine or same pathogen concurrent blood and urine cultures and received at least one	Low RoB	High RoB -Industry-funded: the sponsor of the study (related to one of the studied molecules) were responsible for the study design and conduct of the study; collection, management, analysis and interpretation of the data;

	characteristics at baseline (MITT)				dose of the study drug) resulted in an attrition that was frequent and symmetrical between groups (30% vs 34%).		preparation and review of the manuscript.
Kaye 2019 ZEUS	Low RoB -Randomization (not further detailed) -Comparable patients' characteristics at baseline (mMITT)	Unclear RoB -Not reported	Low RoB -Double-blinded	Low RoB -Double-blinded	Unclear RoB -Early withdrawal after randomisation (mMITT = who had at least one Gram-negative pathogen in urine or same pathogen concurrent blood and urine cultures, and who received at least one dose of the study drug) resulted in an attrition that was relatively frequent and symmetrical between groups (21% vs 23%).	Low RoB	High RoB -Industry-funded: the sponsor of the study (related to one of the studied molecules) provided medical writing support. Authors included employees, members of the company's data monitoring committee and/or received honorarium from the same company.
Kaye 2022 ALLIUM	Low RoB -Computer-generated randomization -Comparable patients' characteristics at baseline (MITT)	Low RoB -Central interactive response system	Low RoB -Double-blinded	Low RoB -Double-blinded	Unclear RoB -Early withdrawal after randomisation (mMITT = who had at least one Gram-negative pathogen in urine or same pathogen concurrent blood and urine cultures and confirmed susceptible to both studied drugs, and who received at least one dose of the study drug) resulted in an attrition that was frequent and symmetrical between groups (34% vs 36%).	Low RoB	High RoB -Industry-funded: the sponsor of the study (related to one of the studied molecules) had a role in the design and conduct of the study; management, analysis, and interpretation of the data; and preparation and review of the manuscript. The sponsor did not have the right to either veto publication or control the decision regarding to which journal the manuscript was submitted.
Naber 2009	Low RoB -Computer-generated randomization -Comparable patients' characteristics at baseline (ITT)	Low RoB -Interactive voice response system	Low RoB -Double-blinded	Low RoB -Double-blinded	High RoB -Early withdrawal after randomisation (CE = who met the definition of cUTI, had a bacterial uropathogen in urine culture, were compliant to study drug or with failure after 3 days of study drug, had no significant protocol deviation) resulted in an attrition that was relatively frequent and asymmetrical between groups (24% vs 29%).	Low RoB	High RoB -Industry-funded: the sponsor of the study (related to one of the studied molecules) but involvement not detailed.
Park 2012	Low RoB -Randomization (not further detailed) -Comparable patients' characteristics at baseline (ITT)	Unclear RoB -Not detailed	Low RoB -Double-blinded	Low RoB -Double-blinded	High RoB -Early withdrawal after randomisation (ME = who met the definition of AP or cUTI, had a baseline pathogen isolated and a follow up urine culture) resulted in an attrition that was very frequent and symmetrical between groups (50% vs 47%).	Unclear RoB -Clinical efficacy was only reported as part of a composite outcome, while microbiological response was reported separately.	High RoB -Industry-funded: the sponsor of the study (related to one of the studied molecules) provided administrative support. Authors included consultants from the same company.
Portsmouth 2018 APEKS	Low RoB -Randomization 2:1 -Comparable patients'	Low RoB -Interactive web/ voice response system	Low RoB -Double-blinded	Low RoB -Double-blinded	Low RoB -Early withdrawal after randomisation (mMITT = who had a qualifying Gram-negative uroppathogen and	Low RoB	High RoB -Industry-funded: the sponsor of the study (related to one of the studied molecules) had a role in the study design, data collection, data analysis, data

	characteristics at baseline (mMITT)				received at least one dose of the study drug) resulted in an attrition that was infrequent and symmetrical between groups (17% vs 20%).		interpretation and writing of the report.
Sims 2017	Low RoB -Block randomization -Comparable patients' characteristics at baseline (ME)	Low RoB -Central interactive voice response system	Low RoB -Double-blinded	Low RoB -Double-blinded	High RoB -Early withdrawal after randomisation (ME = who met the definition of cUT/AP, had at least one Gram-negative and/or anaerobic pathogen in urine culture, and no significant protocol deviation) resulted in an attrition that was relatively frequent and asymmetrical between groups (29% vs 20%).	Low RoB	High RoB -Industry-funded: the sponsor of the study (related to one of the studied molecules) provided medical writing and editorial support. Authors included grantees and employees of the same company.
Sojo-Dorado 2022 FOREST	Unclear RoB -Randomization -Comparable patients' characteristics at baseline, except for more frequent recent invasive procedure of the urinary tract in the fosfomycin group and sample size not reached (MITT)	Unclear RoB -Centrally performed using a previously prepared list integrated in the electronic case report form	High RoB -Investigators were not blinded for drug allocation	Low RoB -Investigators assessing the outcomes were blinded for drug allocation	High RoB -Early withdrawal after randomisation (CE = who had at least one isolated causative bacterial pathogen in a pretreatment urine specimen) in addition to early stoppage of the study resulted in an attrition that was infrequent and very asymmetrical between groups (25% vs 11%).	Low RoB	Low RoB -Not Industry-funded: the sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.
Vasquez 2012	Low RoB -Central randomization -Comparable patients' characteristics at baseline (ITT)	Low RoB -Interactive voice response system	Low RoB -Double-blinded	Low RoB -Double-blinded	High RoB -Early withdrawal after randomisation (CE = who met the definition of cUTI, had a bacterial uropathogen in urine culture, were compliant to study drug or with failure after 2 days of study drug, and had no significant protocol deviation) resulted in an attrition that was very frequent and asymmetrical between groups (59% vs 47%).	Low RoB	High RoB -Industry-funded: the sponsor of the study (related to one of the studied molecules) was not involved in study design, data collection, data analysis, data interpretation, and writing of the report. Authors included employees of the same company.
Wagenlehner 2015 ASPECT-cUTI	Low RoB -Computer-generated block randomization -Comparable patients' characteristics at baseline (mMITT)	Low RoB -Interactive web/ voice response system	Low RoB -Double-blinded	Low RoB -Double-blinded	Unclear RoB -Early withdrawal after randomisation (mMITT = who had at least one uropathogen in urine culture and received at least one dose of the study drug) resulted in an attrition that was relatively frequent and symmetrical between groups (27% vs 26%).	Low RoB	High RoB -Industry-funded: the sponsor of the study (related to one of the studied molecules) was involved in design and conduct of the study, data analysis and interpretation.
Wagenlehner 2016 RECAPTURE 1 and 2	Low RoB -Computer-generated central block randomization -Comparable patients' characteristics at baseline (mMITT)	Low RoB -Interactive web/ voice response system	Low RoB -Double-blinded	Low RoB -Double-blinded	High RoB -Early withdrawal after randomisation (mMITT = who had minimum disease criteria and eligible baseline pathogen) resulted in an attrition that was relatively frequent and	Low RoB	High RoB -Industry-funded: the sponsor of the study (related to one of the studied molecules) provided medical writing support. Authors included employees and contractors of the same company.

					asymmetrical between groups (24% vs 19%).		
Wagenlehner 2019 EPIC	Low RoB -Block randomization by the site pharmacist -Comparable patients' characteristics at baseline (mMITT)	Low RoB -Interactive web/ voice response system	Low RoB -Double-blinded	Low RoB -Double-blinded	Unclear RoB -Early withdrawal after randomisation (mMITT= who had at least one qualifying baseline pathogen confirmed to be susceptible to the studied drugs and received at least one dose of the studied drug) resulted in an attrition that was frequent and symmetrical between groups (37% vs 35%).	Low RoB	High RoB -Industry-funded: the sponsor of the study (related to one of the studied molecules) participated in the study design and data collection and provided medical writing support. Authors included employees, consultants, contractors and advisory board members of the same company.

cUTI: complicated urinary tract infection; AP: acute pyelonephritis; ITT: Intent-to-treat, MITT: Modified Intent-to-treat, mMITT: microbiological Modified Intent-to-treat, CE: Clinically evaluable; ME: Microbiologically evaluable

*Attrition was very frequent in this body of evidence. Attrition was mainly due to early withdrawal after randomisation, caused by restricting the studied population to the mMITT subpopulation (e.g. only using the population that had a confirmed diagnosis of UTI with at least one uropathogen in urine culture). Studies that did not account (or account for sufficiently) for this potential attrition in their sample size calculation might have falsely concluded that the intervention was "not non-inferior" to the comparator (i.e. if the lack of power caused the confidence interval boundaries to cross the non-inferiority margin). Furthermore, without formal analysis of the impact of this withdrawal on the mMITT subpopulation (and acknowledging that baseline characteristics are more likely to be comparable with more imprecision), the risk of bias was difficult to assess, especially when attrition was asymmetrical.

Ceftriaxone / third and fourth generation cephalosporins

Supplementary Table A.3: GRADE Evidence Profile

Question: In patients presenting with complicated UTI, should **Ceftriaxone / third and fourth generation cephalosporins** be used rather than **Any Other Abx** for empirical therapy?

P: In patients with complicated UTI
I: Ceftriaxone / third and fourth generation cephalosporins for empirical therapy
C: Any Other Abx for empirical therapy
Setting: Inpatient and Outpatient

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3rd / 4th generation cephalosporins	Any Other Abx *	Relative (95% CI)	Absolute (95% CI) &		
Combined clinical cure and microbiological response (at End of Follow Up (EFU))												
1[1]	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	62/71 (87.3%)	58/66 (87.9%)	**RR 0.99** (0.88 to 1.13)	**6 fewer per 1,000** (**from 116 fewer** to 105 more)	⊕◯◯◯ Very low	CRITICAL
Microbiological cure (at EFU)												
1[1]	randomised trials	serious[a]	not serious	serious[d]	serious[c]	none	63/71 (88.7%)	58/66 (87.9%)	**RR 1.01** (0.89 to 1.14)	**9 more per 1,000** (from 99 fewer to 116 more)	⊕◯◯◯ Very low	IMPORTANT
Serious Adverse Events												
1[1]	randomised trials	not serious	not serious	not serious	very serious[e]	none	0/135 (0.0%)	0/132 (0.0%)	not estimable	**0 fewer per 1,000**	⊕⊕◯◯ Low	IMPORTANT
Non-Serious Adverse Events												
1[1]	randomised trials	not serious	not serious	not serious	very serious[f]	none	6/135 (4.4%)	14/132 (10.6%)	**RR 0.42** (0.17 to 1.06)	**62 fewer per 1,000** (from 125 fewer to 1 more)	⊕⊕◯◯ Low	IMPORTANT

Notes:
***Any other antibiotics:** Ertapenem (Park 2012)
****Resistance rate at baseline (in analyzed populations):** 0% in 3rd/4th generation cephalosporins group and 0% in comparator group
*****Recurrence of infection, Mortality, Progression of infection, Length of hospital stay and Readmission/ Rehospitalization were not reported (important PIOs).**
&Visual Interpretation of 95% Confidence Interval boundaries for the Absolute Effect: if the lower boundary of the 95% CI is **highlighted in red,** it means it is crossing the non-inferiority margin of 10% (below 100 fewer per 1,000 patients = non-inferior), and if one boundary of the 95% is **highlighted in blue,** it means that it is not crossing the null value for superiority (i.e. confidence interval not including zero = superior or inferior).

CI: confidence interval; **RR:** risk ratio; **Abx**: antibiotics

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect à
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

GRADE domains
Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

Explanations

a. Combined clinical cure and microbiological efficacy at TOC was assessed in the "mMITT" population which was potentially biased by significant attrition bias.

b. The reported outcome is not directly measuring clinical cure, thus rated down for indirectness.
c. Based on an inferiority margin of 10%, not rated down for imprecision, but small sample size and optimal information size criteria not met.
d. Microbiological cure is considered a potential surrogate marker of clinical cure and recurrence of infection, but uncertainty remains around the strength of this association.
e. No event occurring in both groups, optimal information size criteria not met. 95% CI may not include a meaningful difference (i.e., crossing the null value), thus the treatment with treatment A failed to show or exclude a beneficial effect as compared to treatment B.
f. Few events reported, optimal information size criteria not met. 95% CI may not include a meaningful difference (i.e., crossing the null value), thus treatment A failed to show or exclude a beneficial effect as compared to treatment B.

References

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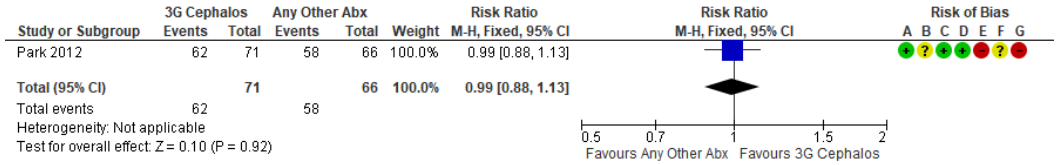
Supplementary Figures A.3: Forest plots for each patient-important outcome

A.3a) Combined clinical cure and microbiological response (at End of Follow Up (EOF))



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.3b) Microbiological cure (at EOF)

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.3c) Serious Adverse Events

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.3d) Non-Serious Adverse Events

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Piperacillin-tazobactam

Supplementary Table A.4: GRADE Evidence Profile

Question: In patients presenting with complicated UTI, should **Piperacillin-tazobactam** be used rather than **Any Other Abx** for empirical therapy?

P: In patients with complicated UTI
I: Piperacillin-Tazobactam for empirical therapy
C: Any Other Abx for empirical therapy
Setting: Inpatient and Outpatient

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Piperacillin-tazobactam	Any Other Abx *	Relative (95% CI)	Absolute (95% CI) [&]		
Clinical cure (at Test-Of-Cure (TOC))												
3[1,2,3]	randomised trials	serious[a]	not serious	not serious	not serious[b]	none	616/693 (88.9%)	660/721 (91.5%)	**RR 0.97** (0.94 to 1.01)	**27 fewer per 1,000** (from 55 fewer to 9 more)	⊕⊕⊕◯ Moderate	CRITICAL
Microbiological cure (at TOC)												
3[1,2,3]	randomised trials	serious[c]	not serious[d]	serious[e]	not serious	none	421/693 (60.8%)	535/721 (74.2%)	**RR 0.81** (0.76 to 0.87)	**141 fewer per 1,000** (from 178 fewer to 96 fewer)	⊕⊕◯◯ Low	IMPORTANT
Recurrence of infection (at Late Follow Up (LFU))												
1[1]	randomised trials	not serious	not serious	not serious	very serious[f]	none	7/178 (3.9%)	8/184 (4.3%)	**RR 0.90** (0.34 to 2.44)	**4 fewer per 1,000** (from 29 fewer to 63 more)	⊕⊕◯◯ Low	IMPORTANT
Mortality												
3[1,2,3]	randomised trials	not serious	not serious	not serious	very serious[f]	none	5/1022 (0.5%)	5/1021 (0.5%)	**RR 1.00** (0.29 to 3.43)	**0 fewer per 1,000** (from 3 fewer to 12 more)	⊕⊕◯◯ Low	IMPORTANT
Serious Adverse Events												
3[1,2,3]	randomised trials	not serious	not serious	not serious	very serious[f]	none	37/1022 (3.6%)	38/1021 (3.7%)	**RR 0.97** (0.62 to 1.52)	**1 fewer per 1,000** (from 14 fewer to 19 more)	⊕⊕◯◯ Low	IMPORTANT
Non-Serious Adverse Events												
3[1,2,3]	randomised trials	not serious	not serious	not serious	not serious	none	413/1022 (40.4%)	482/1021 (47.2%)	**RR 0.86** (0.78 to 0.95)	**66 fewer per 1,000** (from 104 fewer to 24 fewer)	⊕⊕⊕⊕ High	IMPORTANT

Notes:
***Any other antibiotics:** Cefepime-Enmetazobactam (Kaye 2022), IV Fosfomycin (Kaye 2019), and Meropenem-Vaborbactam (Kaye 2018)
****Resistance rate at baseline (in analyzed populations):** ranging from 0% to 10.6% in Piperacillin-Tazobactam group versus 0 to 0.7% in comparator group.
*****Progression of infection, Length of hospital stay and Readmission/ Rehospitalization were not reported (important PIOs).**
[&]**Visual Interpretation of 95% Confidence Interval boundaries for the Absolute Effect**: if the lower boundary of the 95% CI is **highlighted in red,** it means it is crossing the non-inferiority margin of 10% (below 100 fewer per 1,000 patients = non-inferior), and if one boundary of the 95% is **highlighted in blue,** it means that it is not crossing the null value for superiority (i.e. confidence interval not including zero = superior or inferior).

CI: confidence interval; **RR:** risk ratio; **Abx**: antibiotics

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Piperacillin-tazobactam	Any Other Abx *	Relative (95% CI)	Absolute (95% CI) [&]		

GRADE domains

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

Explanations

a. Attrition bias and bias related to the sources of funding were considered potentially significant in most studies included in the analysis.
b. Based on an inferiority margin of 10% (judged clinically significant by the panelists), not rated down for imprecision, but optimal information size criteria not met.
c. Attrition bias (especially in the context of a non-inferiority design) was considered potentially significant in most studies included in the analysis.
d. Not rated down for inconsistency since heterogeneity is likely explained by the various Abx included in the comparator group.
e. Microbiologicalcure is considered a potential surrogate marker of clinical cure and recurrence of infection, but uncertainty remains around the strength of this association.
f. Few events in both groups, optimal information size criteria not met. 95% CI may not include a meaningful difference (i.e. crossing the null value), thus treatment A failed to show or exclude a beneficial effect as compared to treatment B.

References

1.Kaye KS, Rice LB,Dane AL,Stus V,Sagan O,Fedosiuk E,Das AF,Skarinsky D,Eckburg PB,Ellis-Grosse EJ. Fosfomycin for Injection (ZTI-01) Versus Piperacillintazobactam for the Treatment of Complicated Urinary Tract Infection Including Acute Pyelonephritis: ZEUS, A Phase 2/3 Randomized Trial. Clinical Infectious Diseases; 2019.
2.Kaye KS, Bhowmick T,Metallidis S,Bleasdale SC,Sagan OS,Stus V,Vazquez J,Zaitsev V,Bidair M,Chorvat E,Dragoescu PO,Fedosiuk E,Horcajada JP,Murta C,Sarychev Y,Stoev V,Morgan E,Fusaro K,Griffith D,Lomovskaya O,Alexander EL,Loutit J,Dudley MN,Giamarellos-Bourboulis EJ. Effect of Meropenem-Vaborbactam vs Piperacillin-Tazobactam on Clinical Cure or Improvement and Microbial Eradication in Complicated Urinary Tract Infection. JAMA; 2018.
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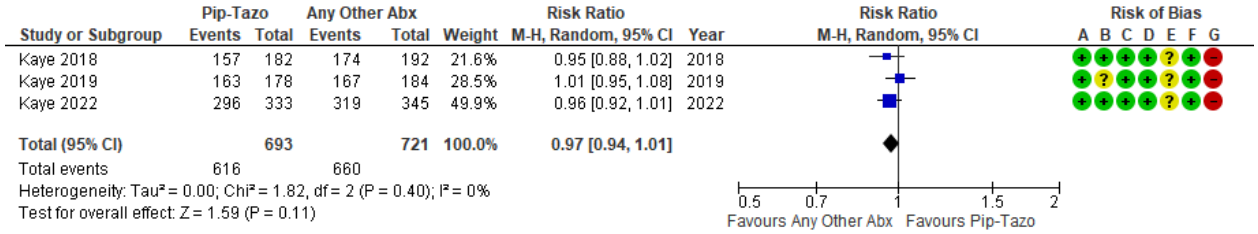
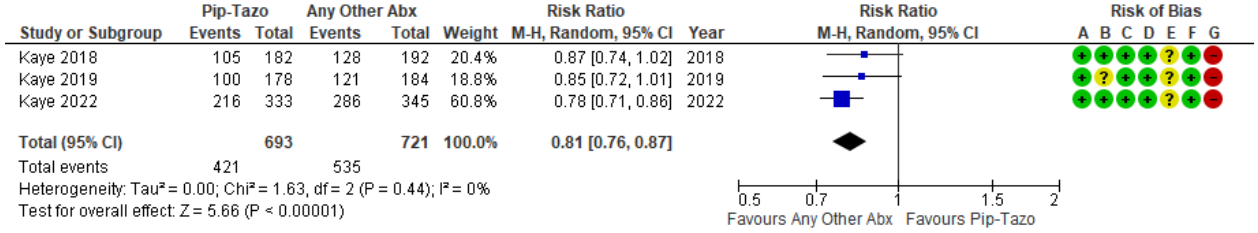
Supplementary Figures A.4: Forest plots for each patient-important outcome

A.4a) Clinical cure (at Test-Of-Cure (TOC))



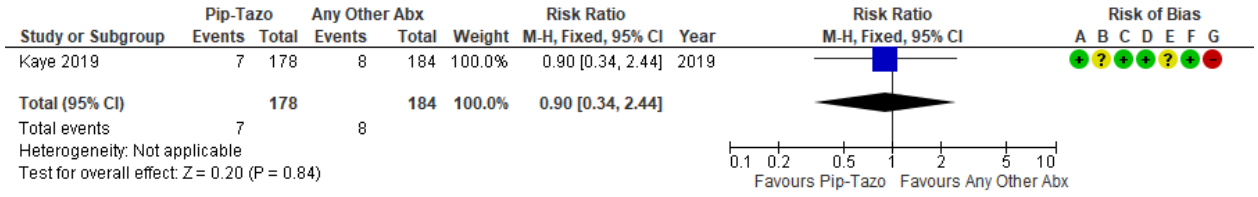
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.4b) Microbiological cure (at TOC)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.4c) Recurrence of Infection (Late Follow Up (LFU))

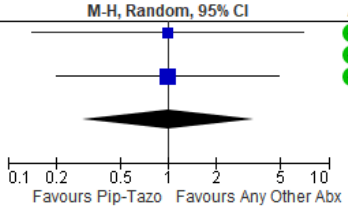


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.4d) Mortality

Study or Subgroup	Pip-Tazo Events	Pip-Tazo Total	Any Other Abx Events	Any Other Abx Total	Weight	Risk Ratio M-H, Random, 95% CI	Year	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Kaye 2018	2	273	2	272	40.0%	1.00 [0.14, 7.02]	2018		+ + + + ? + −
Kaye 2019	0	231	0	233		Not estimable	2019		+ ? + + ? + −
Kaye 2022	3	518	3	516	60.0%	1.00 [0.20, 4.91]	2022		+ + + + ? + −
Total (95% CI)		**1022**		**1021**	**100.0%**	**1.00 [0.29, 3.43]**			
Total events	5		5						

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.01 (P = 1.00)

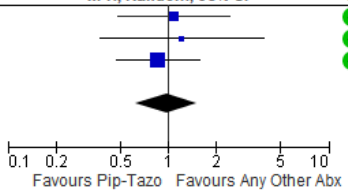


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.4e) Serious Adverse Events

Study or Subgroup	Pip-Tazo Events	Pip-Tazo Total	Any Other Abx Events	Any Other Abx Total	Weight	Risk Ratio M-H, Random, 95% CI	Year	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Kaye 2018	12	273	11	272	30.9%	1.09 [0.49, 2.42]	2018		+ + + + ? + −
Kaye 2019	6	231	5	233	14.4%	1.21 [0.37, 3.91]	2019		+ ? + + ? + −
Kaye 2022	19	518	22	516	54.7%	0.86 [0.47, 1.57]	2022		+ + + + ? + −
Total (95% CI)		**1022**		**1021**	**100.0%**	**0.97 [0.62, 1.52]**			
Total events	37		38						

Heterogeneity: Tau² = 0.00; Chi² = 0.37, df = 2 (P = 0.83); I² = 0%
Test for overall effect: Z = 0.13 (P = 0.90)

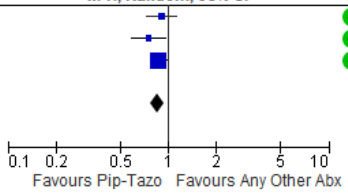


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.4f) Non-Serious Adverse Events

Study or Subgroup	Pip-Tazo Events	Pip-Tazo Total	Any Other Abx Events	Any Other Abx Total	Weight	Risk Ratio M-H, Random, 95% CI	Year	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Kaye 2018	97	273	106	272	19.9%	0.91 [0.73, 1.13]	2018		+ + + + ? + −
Kaye 2019	74	231	99	233	16.4%	0.75 [0.59, 0.96]	2019		+ ? + + ? + −
Kaye 2022	242	518	277	516	63.7%	0.87 [0.77, 0.98]	2022		+ + + + ? + −
Total (95% CI)		**1022**		**1021**	**100.0%**	**0.86 [0.78, 0.95]**			
Total events	413		482						

Heterogeneity: Tau² = 0.00; Chi² = 1.47, df = 2 (P = 0.48); I² = 0%
Test for overall effect: Z = 3.09 (P = 0.002)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Fluoroquinolones

Supplementary Table A.5: GRADE Evidence Profile

Question: In patients presenting with complicated UTI, should **Fluoroquinolones** be used rather than **Any Other Abx** for empirical therapy?

P: In patients with complicated UTI
I: Fluoroquinolones for empirical therapy
C: **Any Other Abx** for empirical therapy
Setting: Inpatient and Outpatient

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluoroquinolones	Any Other Abx *	Relative (95% CI)	Absolute (95% CI) [&]		
Clinical cure (at Test-Of-Cure (TOC))												
3[1,2,3]	randomised trials	serious[a]	not serious	not serious	not serious[b]	none	615/697 (88.2%)	682/747 (91.3%)	**RR 0.96** (0.93 to 0.99)	**37 fewer per 1,000** (from 64 fewer to 9 fewer)	⊕⊕⊕◯ Moderate	CRITICAL
Microbiological cure (at TOC)												
3[1,2,3]	randomised trials	serious[a]	not serious[c]	serious[d]	not serious[b]	none	528/696 (75.9%)	587/741 (79.2%)	**RR 0.96** (0.86 to 1.06)	**32 fewer per 1,000** (from 111 fewer to 48 more)	⊕⊕◯◯ Low	IMPORTANT
Recurrence of infection (at Late Follow Up (LFU))												
1[2]	randomised trials	not serious	not serious	not serious	very serious[e]	none	1/16 (6.3%)	4/28 (14.3%)	**RR 0.44** (0.05 to 3.59)	**80 fewer per 1,000** (from 136 fewer to 370 more)	⊕⊕◯◯ Low	IMPORTANT
Mortality												
3[1,2,3]	randomised trials	not serious	not serious	not serious	very serious[f]	none	0/653 (0.0%)	1/756 (0.1%)	**RR 0.33** (0.01 to 8.13)	**1 fewer per 1,000** (from 1 fewer to 9 more)	⊕⊕◯◯ Low	IMPORTANT
Serious Adverse Events												
3[1,2,3]	randomised trials	not serious	not serious	not serious	serious[g]	none	35/951 (3.7%)	48/1005 (4.8%)	**RR 0.80** (0.45 to 1.40)	**10 fewer per 1,000** (from 26 fewer to 19 more)	⊕⊕⊕◯ Moderate	IMPORTANT
Non-Serious Adverse Events												
3[1,2,3]	randomised trials	not serious	not serious	not serious	serious[g]	none	427/951 (44.9%)	460/1005 (45.8%)	**RR 0.98** (0.87 to 1.10)	**9 fewer per 1,000** (from 60 fewer to 46 more)	⊕⊕⊕◯ Moderate	IMPORTANT

Notes:
***Any other antibiotics:** Plazomicin (Connolly 2018), Ceftolozane-Tazobactam (Wagenlehner 2015) and Doripenem (Naber 2009)
****Resistance rate at baseline (in analyzed populations):** ranging from 14.3-26.7% in fluoroquinolone group and 0.5-7.1% in comparator group
*****Progression of infection, Length of hospital stay and Readmission/ Rehospitalization were not reported (important PIOs).**
[&]**Visual Interpretation of 95% Confidence Interval boundaries for the Absolute Effect**: if the lower boundary of the 95% CI is **highlighted in red,** it means it is crossing the non-inferiority margin of 10% (below 100 fewer per 1,000 patients = non-inferior), and if one boundary of the 95% is **highlighted in blue,** it means that it is not crossing the null value for superiority (i.e. confidence interval not including zero = superior or inferior).

CI: confidence interval; **RR:** risk ratio; **Abx:** antibiotics

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluoroquinolones	Any Other Abx *	Relative (95% CI)	Absolute (95% CI) [&]		

GRADE domains

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

Explanations

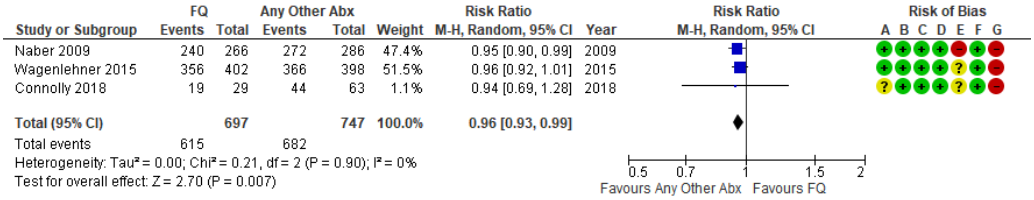
a. Attrition bias and bias related to the sources of funding were considered potentially significant in most studies included in the analysis.
b. Based on an inferiority margin of 10%, not rated down for imprecision.
c. Not rated down for inconsistency since heterogeneity is likely explained by the various Abx included in the comparator group.
d. Microbiological cure is considered to be a potential surrogate marker of clinical cure and recurrence of infection, but uncertainty remains around the strength of this association.
e. Few events in both groups, optimal information size criteria not met (very wide confidence interval). 95% CI may not include a meaningful difference (i.e., crossing the null value), thus treatment A failed to show or exclude a beneficial effect as compared to treatment B.
f. Few events in both groups, optimal information size criteria not met. 95% CI may not include a meaningful difference (i.e., crossing the null value), thus treatment A failed to show or exclude a beneficial effect as compared to treatment B.
g. 95% CI may not include a meaningful difference (i.e., crossing the null value), thus treatment A failed to show or exclude a beneficial effect as compared to treatment B.

References

1.Connolly LE, Riddle V,Cebrik D,Armstrong ES,Miller LG. A Multicenter, Randomized, Double-Blind, Phase 2 Study of the Efficacy and Safety of Plazomicin Compared with Levofloxacin in the Treatment of Complicated Urinary Tract Infection and Acute Pyelonephritis. Antimicrob Agents Chemother; 2018.
2.Wagenlehner FM, Umeh O,Steenbergen J,Yuan G,Darouiche RO. Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: A randomised, double-blind, phase 3 trial (ASPECT-cUTI). The Lancet; 2015.
3.Naber KG, Llorens L,Kaniga K,Kotey P,Hedrich D,Redman R. Intravenous doripenem at 500 milligrams versus levofloxacin at 250 milligrams, with an option to switch to oral therapy, for treatment of complicated lower urinary tract infection and pyelonephritis. Antimicrob Agents Chemother; 2009.
4. Huntington JA, Sakoulas G, Umeh O, Cloutier DJ, Steenbergen JN, Bliss C, Goldstein EJ. Efficacy of ceftolozane/tazobactam versus levofloxacin in the treatment of complicated urinary tract infections (cUTIs) caused by levofloxacin-resistant pathogens: results from the ASPECT-cUTI trial. J Antimicrob Chemother. 2016.

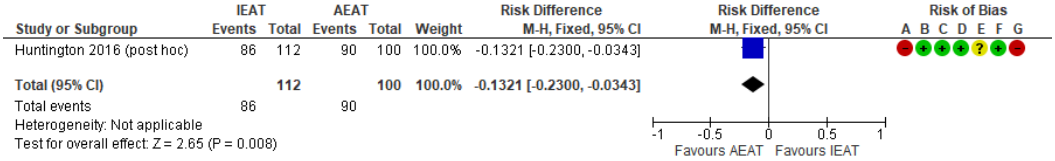
Supplementary Figure A.5: Forest plots for each patient-important outcome

A.5a) Clinical cure (at Test-Of-Cure (TOC))



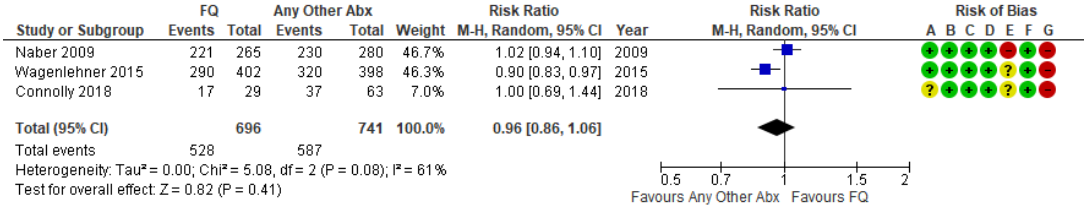
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.5b) Clinical cure in FQ-resistant uropathogens (at TOC)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.5c) Microbiological cure(at TOC)

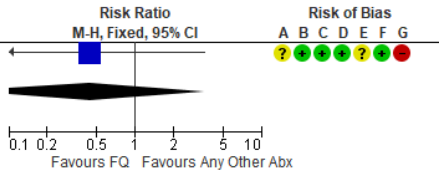


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.5d) Recurrence of infection (Late Follow Up (LFU))

Study or Subgroup	FQ Events	FQ Total	Any Other Abx Events	Any Other Abx Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Connolly 2018	1	16	4	28	100.0%	0.44 [0.05, 3.59]
Total (95% CI)		**16**		**28**	**100.0%**	**0.44 [0.05, 3.59]**
Total events	1		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.77 (P = 0.44)

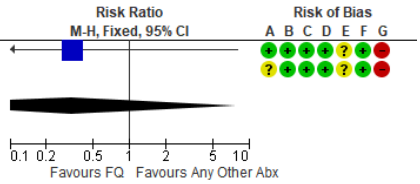


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.5e) Mortality

Study or Subgroup	FQ Events	FQ Total	Any Other Abx Events	Any Other Abx Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Wagenlehner 2015	0	535	1	533	100.0%	0.33 [0.01, 8.13]	2015
Connolly 2018	0	44	0	96		Not estimable	2018
Total (95% CI)		**579**		**629**	**100.0%**	**0.33 [0.01, 8.13]**	
Total events	0		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)

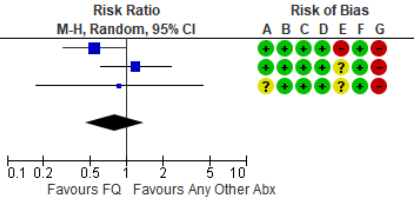


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.5f) Serious Adverse Events

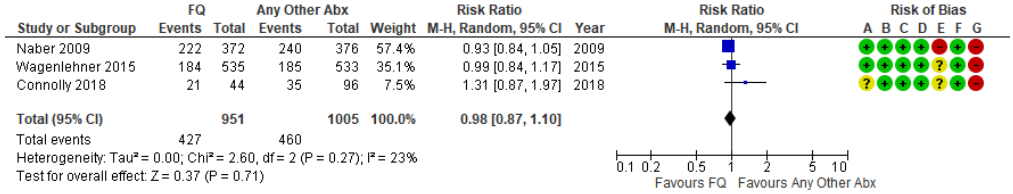
Study or Subgroup	FQ Events	FQ Total	Any Other Abx Events	Any Other Abx Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Naber 2009	15	372	28	376	46.9%	0.54 [0.29, 1.00]	2009
Wagenlehner 2015	18	535	15	533	41.9%	1.20 [0.61, 2.35]	2015
Connolly 2018	2	44	5	96	11.2%	0.87 [0.18, 4.32]	2018
Total (95% CI)		**951**		**1005**	**100.0%**	**0.80 [0.45, 1.40]**	
Total events	35		48				

Heterogeneity: Tau² = 0.08; Chi² = 2.93, df = 2 (P = 0.23); I² = 32%
Test for overall effect: Z = 0.79 (P = 0.43)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.5g) Non-Serious Adverse Events



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Carbapenems (without BLI)

Supplementary Table A.6: GRADE Evidence Profile

Question: In patients presenting with cUTI, should **Carbapenems (without BLI)** be used rather than **Any Other Abx** for empirical therapy?

P: In patients with complicated UTI
I: Carbapenems (without BLI) for empirical therapy
C: **Any Other Abx** for empirical therapy
Setting: Inpatient and Outpatient

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Carbapenems	Any Other Abx *	Relative (95% CI)	Absolute (95% CI) &		
Clinical cure (at TOC)												
7[1,2,3,4,5,6,7]	randomised trials	serious[a]	not serious	not serious	not serious[b]	none	1147/1258 (91.2%)	1209/1345 (89.9%)	**RR 1.02** (0.99 to 1.04)	**18 more per 1,000** (from 9 fewer to 36 more)	⊕⊕⊕◯ Moderate	CRITICAL
Microbiological cure (at TOC)												
7[1,2,3,4,5,6,7]	randomised trials	serious[a]	not serious[c]	serious[d]	not serious[b]	none	911/1251 (72.8%)	1080/1343 (80.4%)	**RR 0.89** (0.83 to 0.97)	**88 fewer per 1,000** (from 137 fewer to 24 fewer)	⊕⊕◯◯ Low	IMPORTANT
Recurrence of infection (Late Follow Up (LFU))												
2[4,7]	randomised trials	not serious	not serious	not serious	very serious[e]	none	26/316 (8.2%)	15/443 (3.4%)	**RR 2.80** (1.46 to 5.38)	**61 more per 1,000** (from 16 more to 148 more)	⊕⊕◯◯ Low	IMPORTANT
Mortality												
4[2,3,4,7]	randomised trials	not serious	not serious	not serious	very serious[f]	none	4/1034 (0.4%)	5/1160 (0.4%)	**RR 0.96** (0.28 to 3.32)	**0 fewer per 1,000** (from 3 fewer to 10 more)	⊕⊕◯◯ Low	IMPORTANT
Serious Adverse Events												
7[1,2,3,4,5,6,7]	randomised trials	not serious	not serious[c]	not serious	serious[g]	none	69/1701 (4.1%)	70/1853 (3.8%)	**RR 1.07** (0.65 to 1.75)	**3 more per 1,000** (from 13 fewer to 28 more)	⊕⊕⊕◯ Moderate	IMPORTANT
Non-Serious Adverse Events												
7[1,2,3,4,5,6,7]	randomised trials	not serious	not serious[c]	not serious	serious[g]	none	658/1686 (39.0%)	683/1841 (37.1%)	**RR 1.10** (0.97 to 1.25)	**37 more per 1,000** (from 11 fewer to 93 more)	⊕⊕⊕◯ Moderate	IMPORTANT

Notes:
***Carbapenems:** Meropenem (Wagenlehner 2019), BAT (Meropenem, Imipenem-cilastatin or Doripenem) (Carmelli 2016), Imipenem-cilastatin (Porthsmouth 2018, Vasquez 2012), Doripenem (Wagenlehner 2016, Naber 2009) and Ertapenm (Park 2012)
****Any other antibiotics:** Plazomicin (Wagenlehner 2019), Cefiderocol (Porthsmouth 2018), Ceftazidime-Avibactam (Carmelli 2016, Vasquez 2012, Wagenlehner 2016), Ceftriaxone (Park 2012), and Levofloxacin (Naber 2009)
*****Resistance rate at baseline (in analyzed populations):** ranging from 0-5.1% in carbapenem group and 0-14.8% in comparator group
******Progression of infection, Length of hospital stay and Readmission/ Rehospitalization were not reported (important PIOs).**
&Visual Interpretation of 95% Confidence Interval boundaries for the Absolute Effect: if the lower boundary of the 95% CI is **highlighted in red,** it means it is crossing the non-inferiority margin of 10% (below 100 fewer per 1,000 patients = non-inferior), and if one boundary of the 95% is **highlighted in blue,** it means that it is not crossing the null value for superiority (i.e. confidence interval not including zero = superior or inferior).

CI: confidence interval; **RR:** risk ratio; **Abx:** antibiotics

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Carbapenems	Any Other Abx *	Relative (95% CI)	Absolute (95% CI) &		

GRADE domains

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

Explanations

a. Attrition bias and bias related to the sources of funding were considered potentially significant in most studies included in the analysis.
b. Based on an inferiority margin of 10%, not rated down for imprecision.
c. Not rated down for inconsistency since heterogeneity is likely due to the different molecules included in the analysis (in the intervention group as well comparator group)
d. Microbiological cure is considered to be a potential surrogate marker of clinical cure and recurrence of infection, but uncertainty remains around the strength of this association.
e. Very few events reported in both groups. Optimal information size criteria not met and the wide 95% CI suggests fragility of the estimate.
f. Very few events reported in both groups. Optimal information size criteria not met. 95% CI may not include a meaningful difference (i.e. crossing the null value), thus the treatment A failed to show or exclude a beneficial effect as compared to treatment B.
g. 95% CI may not include a meaningful difference (i.e. crossing the null value), thus the treatment with treatment A failed to show or exclude a beneficial effect as compared to treatment B.

References

1.Vazquez, J. A.,González Patzán,L. D.,Stricklin,D.,Duttaroy,D. D.,Kreidly,Z.,Lipka,J.,Sable,C.. Efficacy and safety of ceftazidime-avibactam versus imipenem-cilastatin in the treatment of complicated urinary tract infections, including acute pyelonephritis, in hospitalized adults: Results of a prospective, investigator-blinded, randomized study. . Current Medical Research and Opinion; 2012.
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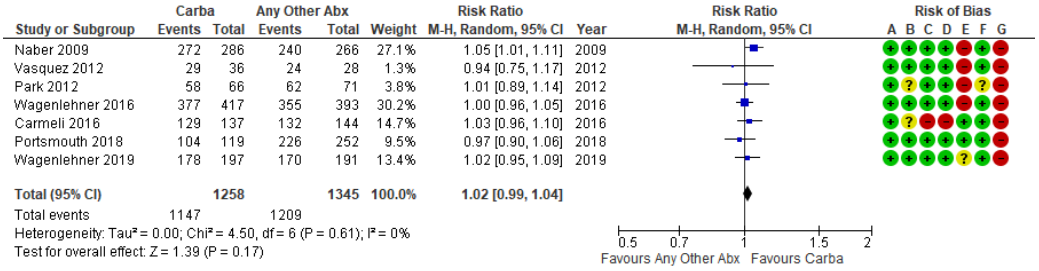
Supplementary Figures A.6: Forest plots for each patient-important outcome

A.6a) Clinical cure (at Test-Of-Cure (TOC))



Study or Subgroup	Carba Events	Carba Total	Any Other Abx Events	Any Other Abx Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Naber 2009	272	286	240	266	27.1%	1.05 [1.01, 1.11]	2009
Vasquez 2012	29	36	24	28	1.3%	0.94 [0.75, 1.17]	2012
Park 2012	58	66	62	71	3.8%	1.01 [0.89, 1.14]	2012
Wagenlehner 2016	377	417	355	393	30.2%	1.00 [0.96, 1.05]	2016
Carmeli 2016	129	137	132	144	14.7%	1.03 [0.96, 1.10]	2016
Portsmouth 2018	104	119	226	252	9.5%	0.97 [0.90, 1.06]	2018
Wagenlehner 2019	178	197	170	191	13.4%	1.02 [0.95, 1.09]	2019
Total (95% CI)		**1258**		**1345**	**100.0%**	**1.02 [0.99, 1.04]**	
Total events	1147		1209				

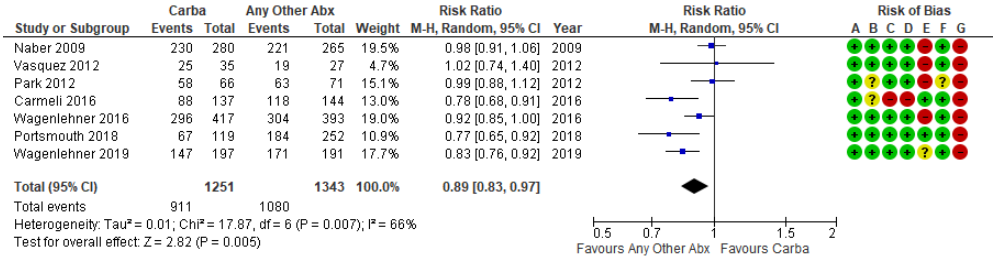
Heterogeneity: Tau² = 0.00; Chi² = 4.50, df = 6 (P = 0.61); I² = 0%
Test for overall effect: Z = 1.39 (P = 0.17)

Risk Ratio M-H, Random, 95% CI
0.5 0.7 1 1.5 2
Favours Any Other Abx Favours Carba

Risk of Bias: A B C D E F G

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.6b) Microbiological cure (at TOC)



Study or Subgroup	Carba Events	Carba Total	Any Other Abx Events	Any Other Abx Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Naber 2009	230	280	221	265	19.5%	0.98 [0.91, 1.06]	2009
Vasquez 2012	25	35	19	27	4.7%	1.02 [0.74, 1.40]	2012
Park 2012	58	66	63	71	15.1%	0.99 [0.88, 1.12]	2012
Carmeli 2016	88	137	118	144	13.0%	0.78 [0.68, 0.91]	2016
Wagenlehner 2016	296	417	304	393	19.0%	0.92 [0.85, 1.00]	2016
Portsmouth 2018	67	119	184	252	10.9%	0.77 [0.65, 0.92]	2018
Wagenlehner 2019	147	197	171	191	17.7%	0.83 [0.76, 0.92]	2019
Total (95% CI)		**1251**		**1343**	**100.0%**	**0.89 [0.83, 0.97]**	
Total events	911		1080				

Heterogeneity: Tau² = 0.01; Chi² = 17.87, df = 6 (P = 0.007); I² = 66%
Test for overall effect: Z = 2.82 (P = 0.005)

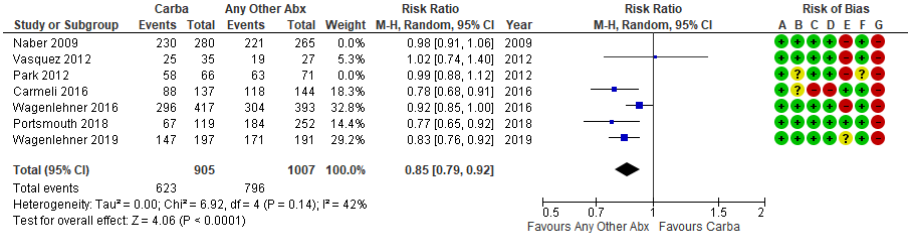
Risk Ratio M-H, Random, 95% CI
0.5 0.7 1 1.5 2
Favours Any Other Abx Favours Carba

Risk of Bias: A B C D E F G

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

1) Subgroup analysis

a) For studies where carbapenems were considered as the comparator of interest



Study or Subgroup	Carba Events	Carba Total	Any Other Abx Events	Any Other Abx Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Naber 2009	230	280	221	265	0.0%	0.98 [0.91, 1.06]	2009
Vasquez 2012	25	35	19	27	5.3%	1.02 [0.74, 1.40]	2012
Park 2012	58	66	63	71	0.0%	0.99 [0.88, 1.12]	2012
Carmeli 2016	88	137	118	144	18.3%	0.78 [0.68, 0.91]	2016
Wagenlehner 2016	296	417	304	393	32.8%	0.92 [0.85, 1.00]	2016
Portsmouth 2018	67	119	184	252	14.4%	0.77 [0.65, 0.92]	2018
Wagenlehner 2019	147	197	171	191	29.2%	0.83 [0.76, 0.92]	2019
Total (95% CI)		**905**		**1007**	**100.0%**	**0.85 [0.79, 0.92]**	
Total events	623		796				

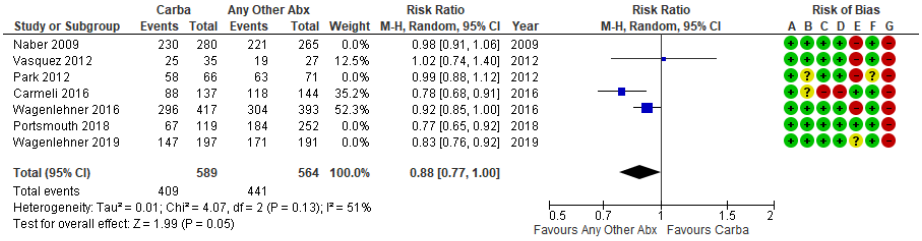
Heterogeneity: Tau² = 0.00; Chi² = 6.92, df = 4 (P = 0.14); I² = 42%
Test for overall effect: Z = 4.06 (P < 0.0001)

Risk Ratio M-H, Random, 95% CI
0.5 0.7 1 1.5 2
Favours Any Other Abx Favours Carba

Risk of Bias: A B C D E F G

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

b) For studies comparing Carbapenems to Ceftazidime-Avibactam

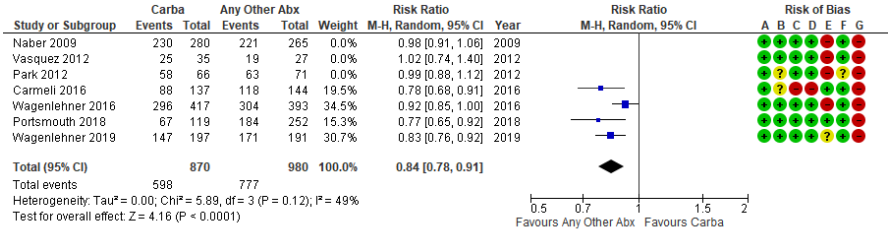


Study or Subgroup	Carba Events	Carba Total	Any Other Abx Events	Any Other Abx Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Naber 2009	230	280	221	265	0.0%	0.98 [0.91, 1.06]	2009
Vasquez 2012	25	35	19	27	12.5%	1.02 [0.74, 1.40]	2012
Park 2012	58	66	63	71	0.0%	0.99 [0.88, 1.12]	2012
Carmeli 2016	88	137	118	144	35.2%	0.78 [0.68, 0.91]	2016
Wagenlehner 2016	296	417	304	393	52.3%	0.92 [0.85, 1.00]	2016
Portsmouth 2018	67	119	184	252	0.0%	0.77 [0.65, 0.92]	2018
Wagenlehner 2019	147	197	171	191	0.0%	0.83 [0.76, 0.92]	2019
Total (95% CI)		**589**		**564**	**100.0%**	**0.88 [0.77, 1.00]**	
Total events	409		441				

Heterogeneity: Tau² = 0.01; Chi² = 4.07, df = 2 (P = 0.13); I² = 51%
Test for overall effect: Z = 1.99 (P = 0.05)

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

c) For studies enrolling after 2012

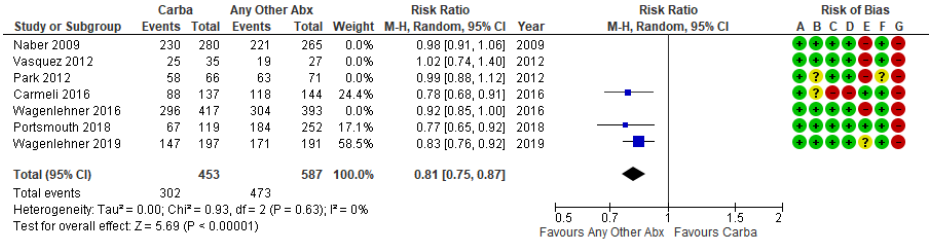


Study or Subgroup	Carba Events	Carba Total	Any Other Abx Events	Any Other Abx Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Naber 2009	230	280	221	265	0.0%	0.98 [0.91, 1.06]	2009
Vasquez 2012	25	35	19	27	0.0%	1.02 [0.74, 1.40]	2012
Park 2012	58	66	63	71	0.0%	0.99 [0.88, 1.12]	2012
Carmeli 2016	88	137	118	144	19.5%	0.78 [0.68, 0.91]	2016
Wagenlehner 2016	296	417	304	393	34.5%	0.92 [0.85, 1.00]	2016
Portsmouth 2018	67	119	184	252	15.3%	0.77 [0.65, 0.92]	2018
Wagenlehner 2019	147	197	171	191	30.7%	0.83 [0.76, 0.92]	2019
Total (95% CI)		**870**		**980**	**100.0%**	**0.84 [0.78, 0.91]**	
Total events	598		777				

Heterogeneity: Tau² = 0.00; Chi² = 5.89, df = 3 (P = 0.12); I² = 49%
Test for overall effect: Z = 4.16 (P < 0.0001)

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

2) *Sensitivity analysis (heterogeneity)*



Study or Subgroup	Carba Events	Carba Total	Any Other Abx Events	Any Other Abx Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Naber 2009	230	280	221	265	0.0%	0.98 [0.91, 1.06]	2009
Vasquez 2012	25	35	19	27	0.0%	1.02 [0.74, 1.40]	2012
Park 2012	58	66	63	71	0.0%	0.99 [0.88, 1.12]	2012
Carmeli 2016	88	137	118	144	24.4%	0.78 [0.68, 0.91]	2016
Wagenlehner 2016	296	417	304	393	0.0%	0.92 [0.85, 1.00]	2016
Portsmouth 2018	67	119	184	252	17.1%	0.77 [0.65, 0.92]	2018
Wagenlehner 2019	147	197	171	191	58.5%	0.83 [0.76, 0.92]	2019
Total (95% CI)		**453**		**587**	**100.0%**	**0.81 [0.75, 0.87]**	
Total events	302		473				

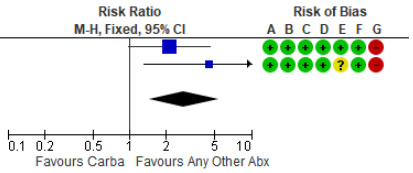
Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 2 (P = 0.63); I² = 0%
Test for overall effect: Z = 5.69 (P < 0.00001)

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.6c) Recurrence of Infection (Late Follow Up (LFU))

Study or Subgroup	Carba Events	Carba Total	Any Other Abx Events	Any Other Abx Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Portsmouth 2018	12	119	12	252	71.6%	2.12 [0.98, 4.57]	2018
Wagenlehner 2019	14	197	3	191	28.4%	4.52 [1.32, 15.49]	2019
Total (95% CI)		**316**		**443**	**100.0%**	**2.80 [1.46, 5.38]**	
Total events	26		15				

Heterogeneity: Chi² = 1.09, df = 1 (P = 0.30); I² = 8%
Test for overall effect: Z = 3.09 (P = 0.002)

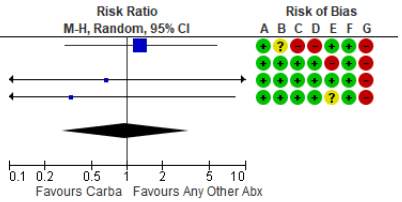


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.6d) Mortality

Study or Subgroup	Carba Events	Carba Total	Any Other Abx Events	Any Other Abx Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Carmeli 2016	4	168	3	164	69.9%	1.30 [0.30, 5.73]	2016
Wagenlehner 2016	0	417	0	393		Not estimable	2016
Portsmouth 2018	0	148	1	300	15.0%	0.67 [0.03, 16.43]	2018
Wagenlehner 2019	0	301	1	303	15.0%	0.34 [0.01, 8.20]	2019
Total (95% CI)		**1034**		**1160**	**100.0%**	**0.96 [0.28, 3.32]**	
Total events	4		5				

Heterogeneity: Tau² = 0.00; Chi² = 0.63, df = 2 (P = 0.73); I² = 0%
Test for overall effect: Z = 0.06 (P = 0.95)

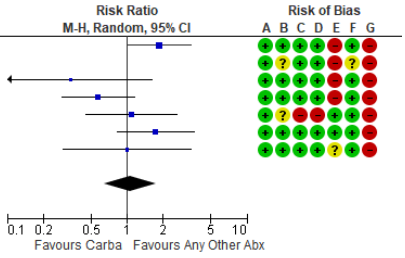


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.6e) Serious Adverse Events

Study or Subgroup	Carba Events	Carba Total	Any Other Abx Events	Any Other Abx Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Naber 2009	28	376	15	372	23.3%	1.85 [1.00, 3.40]	2009
Park 2012	0	132	0	135		Not estimable	2012
Vasquez 2012	2	67	6	68	7.8%	0.34 [0.07, 1.62]	2012
Wagenlehner 2016	12	509	21	511	21.0%	0.57 [0.29, 1.15]	2016
Carmeli 2016	10	168	9	164	16.9%	1.08 [0.45, 2.60]	2016
Portsmouth 2018	12	148	14	300	19.8%	1.74 [0.82, 3.66]	2018
Wagenlehner 2019	5	301	5	303	11.2%	1.01 [0.29, 3.44]	2019
Total (95% CI)		**1701**		**1853**	**100.0%**	**1.07 [0.65, 1.75]**	
Total events	69		70				

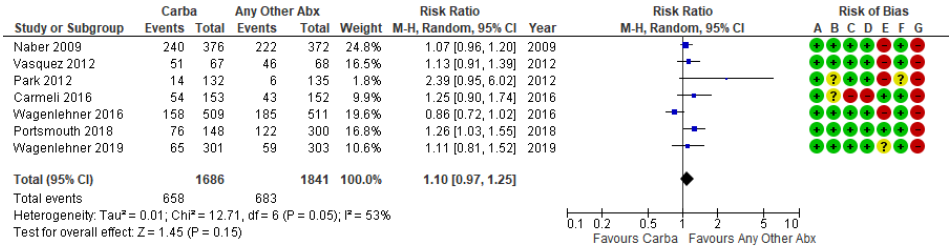
Heterogeneity: Tau² = 0.18; Chi² = 9.72, df = 5 (P = 0.08); I² = 49%
Test for overall effect: Z = 0.26 (P = 0.79)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

à

A.6f) Non-Serious Adverse Events



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Novel beta-lactam/beta-lactamase inhibitors (BLBLI)

Supplementary Table A.7: GRADE Evidence Profile

Question: In patients presenting with cUTI, should **novel BLBLI** be used rather than **Any Other Abx** for empirical therapy?

P: In patients with complicated UTI
I: Novel BLBLI for empirical therapy
C: **Any Other Abx** for empirical therapy
Setting: Inpatient and Outpatient

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Novel BLBLIs *	Any Other Abx **	Relative (95% CI)	Absolute (95% CI) &		
Clinical cure (at Test-Of-Cure (TOC) or earlier assessment)												
7[1,2,3,4,5,6,7]	randomised trials	serious[a]	not serious	not serious	not serious[b]	none	1517/1650 (91.9%)	1423/1587 (89.7%)	**RR 1.01** (0.99 to 1.04)	**9 more per 1,000** (from 9 fewer to 36 more)	⊕⊕⊕◯ Moderate	CRITICAL
Microbiological cure (at TOC or earlier assessment)												
7[1,2,3,4,5,6,7]	randomised trials	serious[a]	not serious[c]	serious[d]	not serious[b]	none	1312/1655 (79.3%)	1095/1587 (69.0%)	**RR 1.12** (1.02 to 1.23)	**83 more per 1,000** (from 14 more to 159 more)	⊕⊕◯◯ Low	IMPORTANT
Mortality												
6[1,3,4,5,6,7]	randomised trials	not serious	not serious	not serious	very serious[e]	none	9/2076 (0.4%)	9/2011 (0.4%)	**RR 0.99** (0.40 to 2.46)	**0 fewer per 1,000** (from 3 fewer to 7 more)	⊕⊕◯◯ Low	IMPORTANT
Serious Adverse Events												
7[1,2,3,4,5,6,7]	randomised trials	not serious	not serious	not serious	serious[f]	none	88/2262 (3.9%)	76/2170 (3.5%)	**RR 1.12** (0.82 to 1.52)	**4 more per 1,000** (from 6 fewer to 18 more)	⊕⊕⊕◯ Moderate	IMPORTANT
Non-Serious Adverse Events												
7[1,2,3,4,5,6,7]	randomised trials	not serious	not serious[c]	not serious	serious[f]	none	899/2250 (40.0%)	816/2155 (37.9%)	**RR 1.04** (0.95 to 1.15)	**15 more per 1,000** (from 19 fewer to 57 more)	⊕⊕⊕◯ Moderate	IMPORTANT

Notes:
***Novel Beta-Lactamase / Beta-Lactamse Inhibitor (BLIBL):** Cefepime-Enmetazobactam (Kaye 2022), Meropenem-Vaborbactam (Kaye 2018), Imipenem-cilastatin-Relabactam (Sims 2017), Ceftazidime-Avibactam (Carmelli 2016, Vasquez 2012, Wagenlehner 2016), and Ceftolozane-Tazobactam (Wageblehner 2015)
****Any other antibiotics:** Piperacillin-Tazobactam (Kaye 2018 and Kaye 2022), Imipenem-cilastatin (Sims 2017, Vasquez 2012), Doripenem (Wagenlehner 2016), and BAT (Meropenem, Imipenem-cilastatin or Doripenem) (Carmelli 2016), and Levofloxacin (Wagenlehner 2015)
*****Resistance rate at baseline (in analyzed populations):** ranging from 0-6.8% in BLIBL group and 0-26.7% in comparator group
******Recurrence of infection, Progression of infection, Length of hospital stay and Readmission/ Rehospitalization were not reported (important PIOs).**
&Visual Interpretation of 95% Confidence Interval boundaries for the Absolute Effect: if the lower boundary of the 95% CI is **highlighted in red,** it means it is crossing the non-inferiority margin of 10% (below 100 fewer per 1,000 patients = non-inferior), and if one boundary of the 95% is **highlighted in blue,** it means that it is not crossing the null value for superiority (i.e. confidence interval not including zero = superior or inferior).

CI: confidence interval; **RR:** risk ratio; **Abx**: Antibiotics

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Novel BLBLIs *	Any Other Abx **	Relative (95% CI)	Absolute (95% CI) &		

GRADE domains

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

Explanations

a. Attrition bias and bias related to the sources of funding were considered potentially significant in most studies included in the analysis.
b. Based on an inferiority margin of 10%, not rated down for imprecision.
c. Not rated down for inconsistency since heterogeneity is likely due to the different molecules included in the analysis (in the intervention group as well comparator group)
d. Microbiological cure is considered to be a potential surrogate marker of clinical cure and recurrence of infection, but uncertainty remains around the strength of this association.
e. Very few events reported in both groups. optimal information size criteria not met. 95% CI may not include a meaningful difference (i.e. crossing the null value), thus the treatment A failed to show or exclude a beneficial effect as compared to treatment B.
f. 95% CI may not include a meaningful difference (i.e. crossing the null value), thus the treatment with treatment A failed to show or exclude a beneficial effect as compared to treatment B.

References

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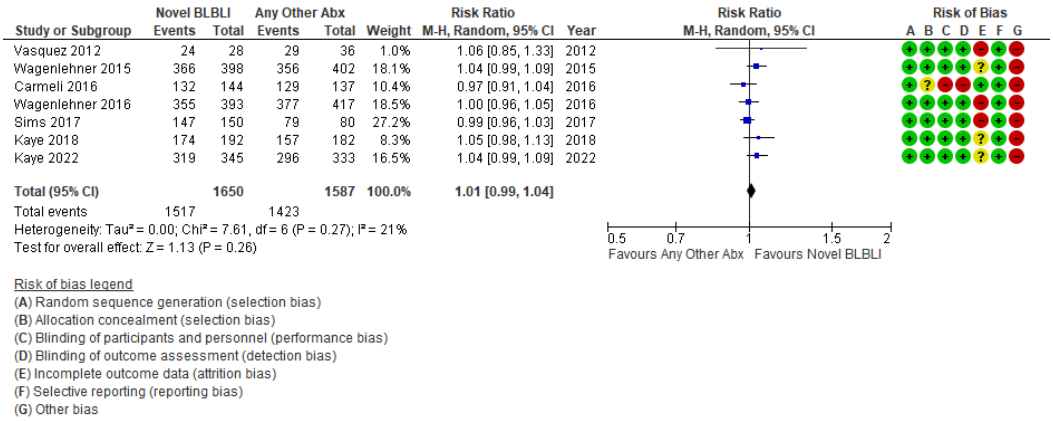
Supplementary Figures A.7: Forest plots for each patient-important outcome

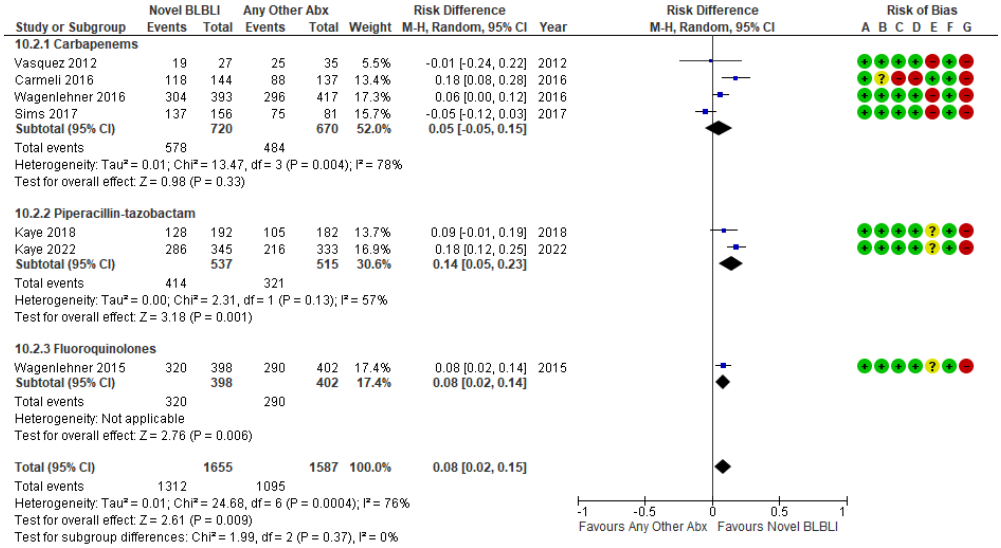
A.7a) Clinical cure (at Test-Of-Cure (TOC) or earlier assessment)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

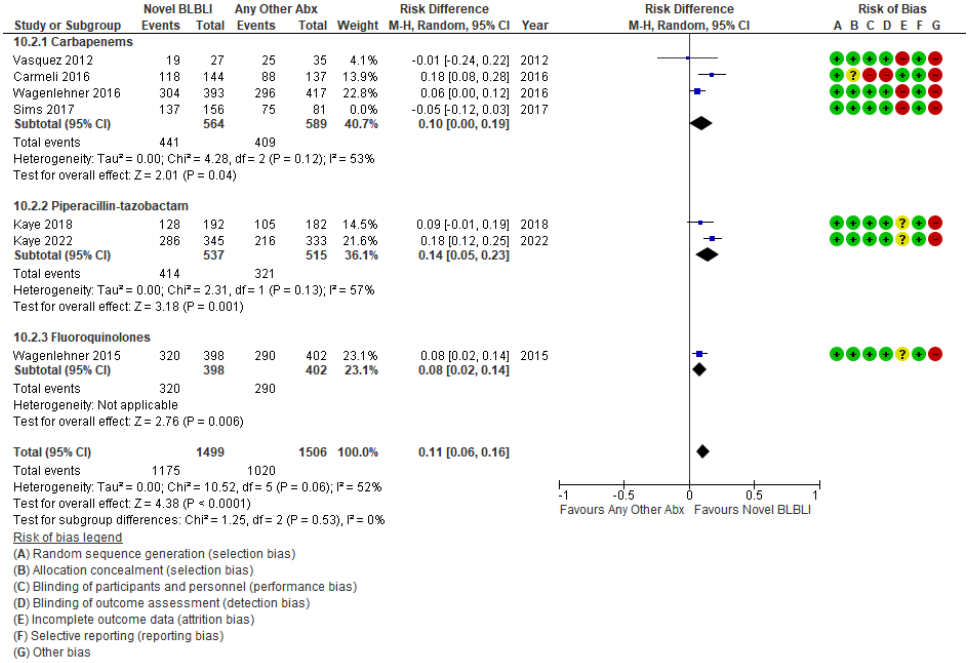
A.7b) Microbiological cure (at TOC or earlier assessment)

1) Subgroup analysis per class of molecules in the comparator group

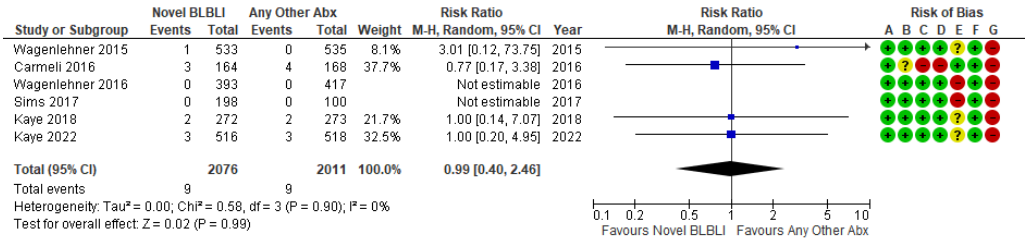


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

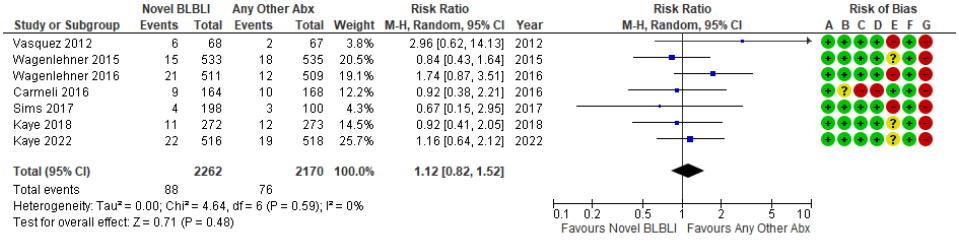
2) Sensitivity analysis (heterogeneity)



A.7c) Mortality



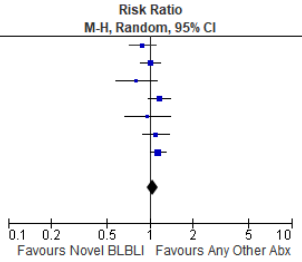
A.7d) Serious Adverse Events

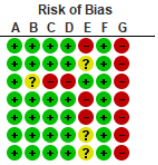


A.7e) Non-Serious Adverse Events

Study or Subgroup	Novel BLBLI Events	Novel BLBLI Total	Any Other Abx Events	Any Other Abx Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Vasquez 2012	46	68	51	67	13.4%	0.89 [0.72, 1.10]	2012
Wagenlehner 2015	185	533	184	535	18.6%	1.01 [0.86, 1.19]	2015
Carmeli 2016	43	152	54	153	6.7%	0.80 [0.58, 1.12]	2016
Wagenlehner 2016	185	511	158	509	17.5%	1.17 [0.98, 1.39]	2016
Sims 2017	57	198	30	100	5.5%	0.96 [0.66, 1.39]	2017
Kaye 2018	106	272	97	273	12.9%	1.10 [0.88, 1.36]	2018
Kaye 2022	277	516	242	518	25.4%	1.15 [1.02, 1.30]	2022
Total (95% CI)		**2250**		**2155**	**100.0%**	**1.04 [0.95, 1.15]**	
Total events	899		816				

Heterogeneity: Tau² = 0.00; Chi² = 8.95, df = 6 (P = 0.18); I² = 33%
Test for overall effect: Z = 0.91 (P = 0.36)





Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Cefiderocol

Supplementary Table A.8: GRADE Evidence Profile

Question: In patients presenting with cUTI, should **Cefiderocol** be used rather than **Any Other Abx** for empirical therapy?

P: In patients with complicated UTI
I: Cefiderocol for empirical therapy
C: Any Other Abx for empirical therapy
Setting: Inpatient and Outpatient

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cefiderocol	Any Other Abx	Relative (95% CI)	Absolute (95% CI) [&]		
Clinical cure (at Test-Of-Cure (TOC))												
2[1,2]	randomised trials	serious[a]	not serious	not serious	not serious[b]	none	238/269 (88.5%)	107/124 (86.3%)	**RR 1.03** (0.95 to 1.12)	**26 more per 1,000** (from 43 fewer to 104 more)	⊕⊕⊕◯ Moderate	CRITICAL
Microbiological cure (at TOC)												
2[1,2]	randomised trials	serious[a]	not serious	serious[c]	not serious[b]	none	196269 (72.9%)	68/124 (54.8%)	**RR 1.33** (1.12 to 1.59)	**181 more per 1,000** (from 66 more to 324 more)	⊕⊕◯◯ Low	IMPORTANT
Recurrence of infection (at Late Follow Up (LFU))												
2[1,2]	randomised trials	not serious	not serious	not serious	very serious[d]	none	13/269 (4.8%)	12/124 (9.7%)	**RR 0.50** (0.24 to 1.04)	**48 fewer per 1,000** (from 74 fewer to 4 more)	⊕⊕◯◯ Low	IMPORTANT
Mortality												
2[1,2]	randomised trials	not serious	not serious	not serious	very serious[d]	none	5/326 (1.5%)	2/158 (1.3%)	**RR 0.90** (0.23 to 3.60)	**3 more per 1,000** (from 3 fewer to 10 more)	⊕⊕◯◯ Low	IMPORTANT
Serious Adverse Events												
2[1,2]	randomised trials	not serious	not serious	not serious	very serious[d]	none	24/326 (7.4%)	17/158 (10.8%)	**RR 0.64** (0.36 to 1.11)	**39 fewer per 1,000** (from 69 fewer to 12 more)	⊕⊕◯◯ Low	IMPORTANT
Non-Serious Adverse Events												
2[1,2]	randomised trials	not serious	not serious	not serious	serious[e]	none	127/326 (39.0%)	80/158 (50.6%)	**RR 0.78** (0.63 to 0.95)	**111 fewer per 1,000** (from 187 fewer to 25 fewer)	⊕⊕⊕◯ Moderate	IMPORTANT

Notes:
***Any other antibiotics:** BAT (mostly colistin based regimen) (Bassetti 2021) and Imipenem-cilastatin **(**Portsmouth 2018)
****Resistance rate at baseline (in analyzed populations):** 0% in Cefiderocol group and 3.8% in comparator group (in Portsmouth 2018 only)
*****Progression of infection, Length of hospital stay and Readmission/ Rehospitalization were not reported (important PIOs).**
[&]Visual Interpretation of 95% Confidence Interval boundaries for the Absolute Effect: if the lower boundary of the 95% CI is **highlighted in red,** it means it is crossing the non-inferiority margin of 10% (below 100 fewer per 1,000 patients = non-inferior), and if one boundary of the 95% is **highlighted in blue,** it means that it is not crossing the null value for superiority (i.e. confidence interval not including zero = superior or inferior).

CI: confidence interval; **RR:** risk ratio; **Abx**: antibiotics

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cefiderocol	Any Other Abx	Relative (95% CI)	Absolute (95% CI) [&]		

GRADE domains

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

Explanations

a. Bias related to the sources of funding was considered potentially significant. One of the 2 trials included is at high risk of bias mainly due to the unblinded design that could have biased the occurrence, the measurement, or the interpretation of outcomes.
b. Based on an inferiority margin of 10% (judged clinically significant by the panelists), not rated down for imprecision.
c. Microbiological cure is considered to be a potential surrogate marker of clinical cure and recurrence of infection, but uncertainty remains around the strength of this association.
d. Few events, optimal information size criteria not met and 95% CI may not include a meaningful difference (i.e. crossing the null value), thus treatment A failed to show or exclude a beneficial effect as compared to treatment B.
e. Small sample size in the control group suggests the potential for fragility in the estimate, making the estimate highly uncertain.

References

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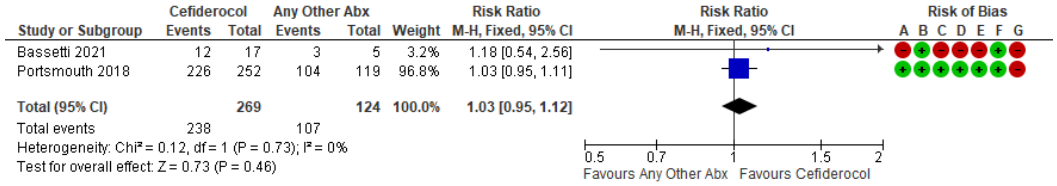
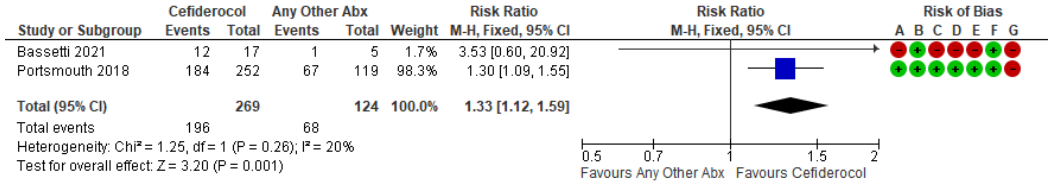
Supplementary Figures A.8: Forest plots for each patient-important outcome

A.8a) Clinical cure (at Test-Of-Cure (TOC))



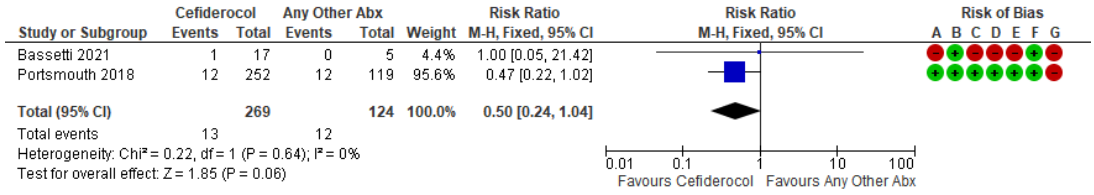
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.8b) Microbiological cure (at TOC)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.8c) Recurrence of Infection (at Late Follow Up (LFU))

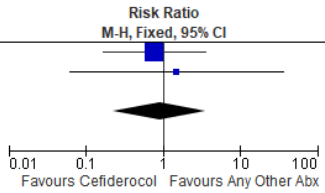


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.8d) Mortality

Study or Subgroup	Cefiderocol Events	Cefiderocol Total	Any Other Abx Events	Any Other Abx Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bassetti 2021	4	26	2	10	81.2%	0.77 [0.17, 3.56]
Portsmouth 2018	1	300	0	148	18.8%	1.49 [0.06, 36.24]
Total (95% CI)		**326**		**158**	**100.0%**	**0.90 [0.23, 3.60]**
Total events	5		2			

Heterogeneity: Chi² = 0.14, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.14 (P = 0.89)

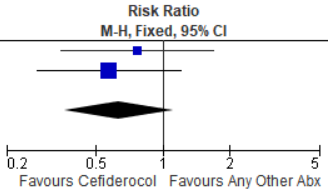


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.8e) Serious Adverse Events

Study or Subgroup	Cefiderocol Events	Cefiderocol Total	Any Other Abx Events	Any Other Abx Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bassetti 2021	10	26	5	10	31.0%	0.77 [0.35, 1.69]
Portsmouth 2018	14	300	12	148	69.0%	0.58 [0.27, 1.21]
Total (95% CI)		**326**		**158**	**100.0%**	**0.64 [0.36, 1.11]**
Total events	24		17			

Heterogeneity: Chi² = 0.29, df = 1 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.59 (P = 0.11)

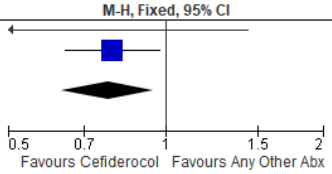


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.8f) Non-Serious Adverse Events

Study or Subgroup	Cefiderocol Events	Cefiderocol Total	Any Other Abx Events	Any Other Abx Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bassetti 2021	5	26	4	10	5.4%	0.48 [0.16, 1.44]
Portsmouth 2018	122	300	76	148	94.6%	0.79 [0.64, 0.98]
Total (95% CI)		**326**		**158**	**100.0%**	**0.78 [0.63, 0.95]**
Total events	127		80			

Heterogeneity: Chi² = 0.77, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 2.44 (P = 0.01)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Plazomicin

Supplementary Table A.9: GRADE Evidence Profile

Question: In patients presenting with cUTI, should Plazomicin be used rather than **Any Other Abx** for empirical therapy?

P: In patients with complicated UTI
I: Plazomicin for empirical therapy
C: Any Other Abx for empirical therapy
Setting: Inpatient and Outpatient

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Plazomicin	Any Other Abx *	Relative (95% CI)	Absolute (95% CI) &		
Clinical cure (at Test-Of-Cure (TOC))												
2[1,2]	randomised trials	serious[a]	not serious	not serious	not serious[b]	none	214/254 (84.3%)	197/226 (87.2%)	**RR 1.00** (0.93 to 1.07)	**0 fewer per 1,000** (from 61 fewer to 61 more)	⊕⊕⊕◯ Moderate	CRITICAL
Microbiological cure (at TOC)												
2[1,2]	randomised trials	serious[a]	not serious	serious[c]	not serious[b]	none	208/254 (81.9%)	164/226 (72.6%)	**RR 1.17** (1.07 to 1.29)	**123 more per 1,000** (from 51 more to 210 more)	⊕⊕◯◯ Low	IMPORTANT
Recurrence of infection (at Late Follow Up (LFU))												
2[1,2]	randomised trials	not serious	not serious[d]	not serious	very serious[e]	none	7/219 (3.2%)	15/213 (7.0%)	**RR 0.40** (0.15 to 1.02)	**42 fewer per 1,000** (from 60 fewer to 1 more)	⊕⊕◯◯ Low	IMPORTANT
Mortality												
2[1,2]	randomised trials	not serious	not serious	not serious	very serious[e]	none	1/399 (0.3%)	0/345 (0.0%)	not estimable	**3 more per 1,000** (from 2 fewer to 7 more)	⊕⊕◯◯ Low	IMPORTANT
Serious Adverse Events												
2[1,2]	randomised trials	not serious	not serious	not serious	very serious[e]	none	10/399 (2.5%)	7/345 (2.0%)	**RR 1.05** (0.40 to 2.77)	**1 more per 1,000** (from 12 fewer to 36 more)	⊕⊕◯◯ Low	IMPORTANT
Non-Serious Adverse Events												
2[1,2]	randomised trials	not serious	not serious	not serious	serious[g]	none	94/399 (23.6%)	86/345 (24.9%)	**RR 0.86** (0.67 to 1.11)	**35 fewer per 1,000** (from 82 fewer to 27 more)	⊕⊕⊕◯ Moderate	IMPORTANT

Notes:
***Any other antibiotics:** Meropenem (Wagenlehner 2019) and Levofloxacin (Connolly 2018)
****Resistance rate at baseline (in analyzed populations):** ranging from 0-7.1% in Plazomicin group and 0-14.3% in comparator group
*****Progression of infection, Length of hospital stay and Readmission/ Rehospitalization were not reported (important PIOs).**
&Visual Interpretation of 95% Confidence Interval boundaries for the Absolute Effect: if the lower boundary of the 95% CI is **highlighted in red,** it means it is crossing the non-inferiority margin of 10% (below 100 fewer per 1,000 patients = non-inferior), and if one boundary of the 95% is **highlighted in blue,** it means that it is not crossing the null value for superiority (i.e. confidence interval not including zero = superior or inferior).

CI: confidence interval; **RR:** risk ratio; **Abx:** antibiotics

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Plazomicin	Any Other Abx *	Relative (95% CI)	Absolute (95% CI) &		

GRADE domains

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

Explanations

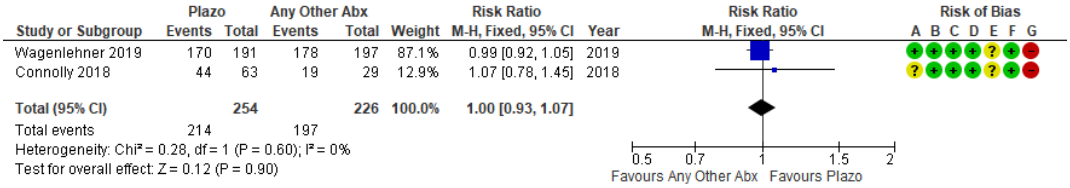
a. Attrition bias and bias related to the sources of funding were considered potentially significant in most studies included in the analysis.
b. Based on an inferiority margin of 10% (judged clinically significant by the panelists), not rated down for imprecision.
c. Microbiological cure is considered to be a potential surrogate marker of clinical cure and recurrence of infection, but uncertainty remains around the strength of this association.
d. Not rated down for inconsistency since heterogeneity is likely explained by the various Abx included in the comparator group.
e. Few events in both groups, optimal information size criteria not met. 95% CI may not include a meaningful difference (i.e. crossing the null value), thus treatment A failed to show or exclude a beneficial effect as compared to treatment B.
f. No events in the control group., optimal information size criteria not met. 95% CI may not include a meaningful difference (i.e. crossing the null value), thus treatment A failed to show or exclude a beneficial effect as compared to treatment B.
g. 95% CI may not include a meaningful difference (i.e. crossing the null value), thus treatment A failed to show or exclude a beneficial effect as compared to treatment B.

References

1.Wagenlehner FME, Cloutier DJ,Komirenko AS,Cebrik DS,Krause KM,Keepers TR,Connolly LE,Miller LG,Friedland I,Dwyer JP,for the EPIC Study Group. Once-Daily Plazomicin for Complicated Urinary Tract Infections. NEJM; 2019.
2.Connolly LE, Riddle V,Cebrik D,Armstrong ES,Miller LG. A Multicenter, Randomized, Double-Blind, Phase 2 Study of the Efficacy and Safety of Plazomicin Compared with Levofloxacin in the Treatment of Complicated Urinary Tract Infection and Acute Pyelonephritis. Antimicrob Agents Chemother; 2018.

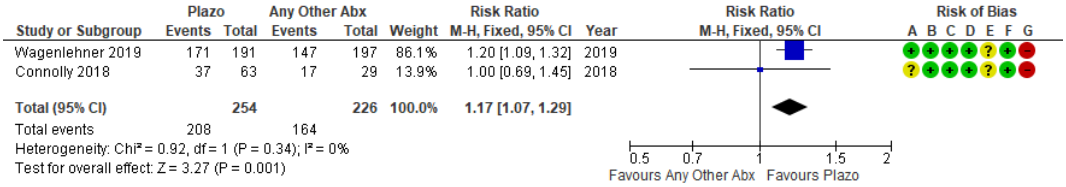
Supplementary Figures A9: Forest plots for each patient-important outcome

A.9a) Clinical cure (at Test-Of-Cure (TOC))



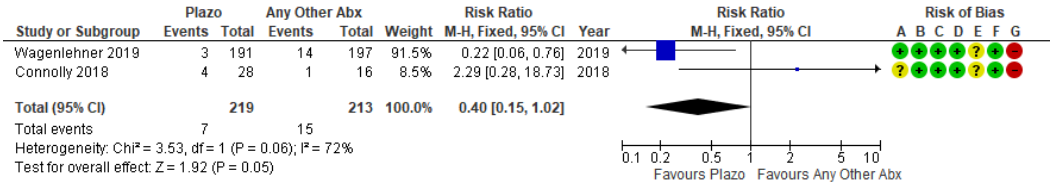
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.9b) Microbiological cure (at TOC)



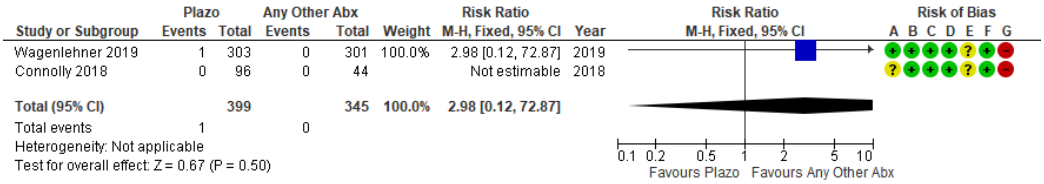
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.9c) Recurrence of Infection (at Late Follow Up (LFU))



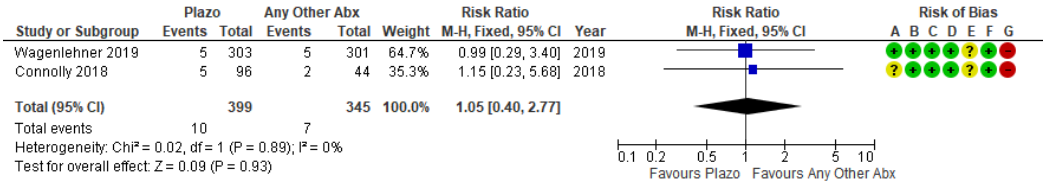
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.9d) Mortality



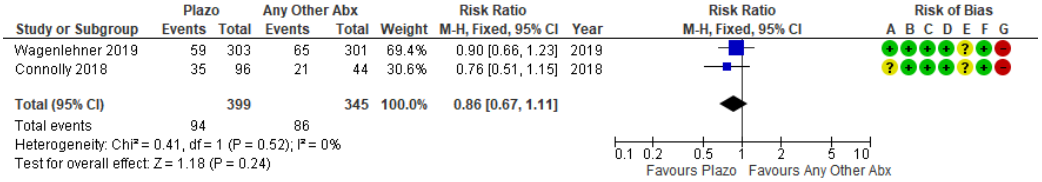
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.9e) Serious Adverse Events



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.9f) Non-Serious Adverse Events



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

IV Fosfomycin

Supplementary Table A.10: GRADE Evidence Profile

Question: In patients presenting with cUTI, should IV **Fosfomycin** be used rather than **Any Other Abx** for empirical therapy?

P: In patients with complicated UTI
I: Fosfomycin for empirical therapy
C: Any other Abx for empirical therapy
Setting: Inpatient and Outpatient

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fosfomycin	Any Other Abx *	Relative (95% CI)	Absolute (95% CI) [&]		
Clinical cure (at Test-Of-Cure (TOC))												
2[1,2]	randomised trials	serious[a]	not serious[b]	not serious	not serious[c]	none	226/245 (92.2%)	227/249 (91.2%)	**RR 1.01** (0.96 to 1.06)	**9 more per 1,000** (from 36 fewer to 55 more)	⊕⊕⊕◯ Moderate	CRITICAL
Microbiological cure (at TOC)												
2[1,2]	randomised trials	serious[a]	not serious[b]	serious[d]	not serious[c]	none	169/242 (69.8%)	159/247 (64.4%)	**RR 1.10** (0.97 to 1.24)	**64 more per 1,000** (from 19 fewer to 154 more)	⊕⊕◯◯ Low	IMPORTANT
Recurrence of infection (at Late Follow Up (LFU))												
2[1,2]	randomised trials	serious[a]	not serious	not serious	very serious[e]	none	16/245 (6.5%)	13/249 (5.2%)	**RR 1.30** (0.64 to 2.63)	**16 more per 1,000** (from 19 fewer to 85 more)	⊕◯◯◯ Very low	IMPORTANT
Mortality												
2[1,2]	randomised trials	serious[f]	not serious	not serious	very serious[g]	none	2/294 (0.7%)	2/302 (0.7%)	**RR 1.16** (0.17 to 8.02)	**1 more per 1,000** (from 5 fewer to 46 more)	⊕◯◯◯ Very low	IMPORTANT
Serious Adverse Events												
2[1,2]	randomised trials	serious[a]	not serious[b]	not serious	very serious[e]	none	11/303 (3.6%)	6/304 (2.0%)	**RR 1.78** (0.69 to 4.59)	**15 more per 1,000** (from 6 fewer to 71 more)	⊕◯◯◯ Very low	IMPORTANT
Non-Serious Adverse Events												
1[1]	randomised trials	serious[h]	not serious	not serious	serious[i]	none	99/233 (42.5%)	74/231 (32.0%)	**RR 1.33** (1.04 to 1.69)	**106 more per 1,000** (from 13 more to 221 more)	⊕⊕◯◯ Low	IMPORTANT

Notes:
***Any other antibiotics:** Ceftriaxone or Meropenem (Sojo-Dorado 2022) and Piperacillin-Tazobactam (Kaye 2019)
****Resistance rate at baseline (in analyzed populations):** ranging from 0% in Fosfomycin group and 0-10.2% in comparator group
*****Progression of infection, Length of hospital stay and Readmission/ Rehospitalization were not reported (important PIOs).**
[&]Visual Interpretation of 95% Confidence Interval boundaries for the Absolute Effect: if the lower boundary of the 95% CI is **highlighted in red,** it means it is crossing the non-inferiority margin of 10% (below 100 fewer per 1,000 patients = non-inferior), and if one boundary of the 95% is **highlighted in blue,** it means that it is not crossing the null value for superiority (i.e. confidence interval not including zero = superior or inferior).

CI: confidence interval; **RR:** risk ratio; **Abx**: antibiotics

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fosfomycin	Any Other Abx *	Relative (95% CI)	Absolute (95% CI) &		

GRADE domains

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

Explanations

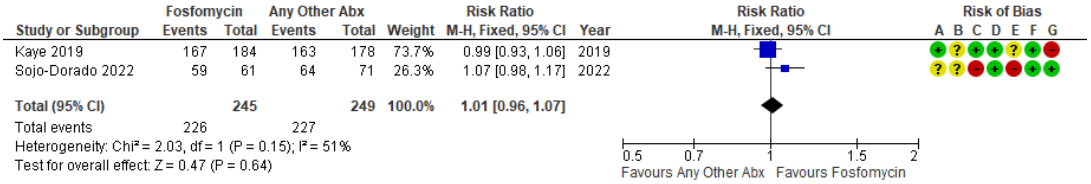
a. Attrition bias and bias related to the sources of funding were considered potentially significant in one of the studies included in the analysis. Early stoppage with attrition bias as well as partial unblinded design in one trial (which can affect the outcome of interest that require judgment, such as how investigators judge clinical improvement) were also judged significant.
b. Not rated down for inconsistency since heterogeneity is likely due to the different molecules included in the analysis (in the intervention group as well comparator group)
c. Based on an inferiority margin of 10% (judged clinically significant by the panelists), not rated down for imprecision, but optimal information size criteria not met.
d. Microbiological cure is considered to be a potential surrogate marker of clinical cure and recurrence of infection, but uncertainty remains around the strength of this association.
e. Few events in both groups, optimal information size criteria not met. 95% CI may not include a meaningful difference (i.e. crossing the null value), thus treatment A failed to show or exclude a beneficial effect as compared to treatment B.
f. Early stoppage with attrition bias as well as partial unblinded design (which can affect the outcome of interest that require judgment, such as how investigators judge clinical improvement) were also judged significant.
g. No event in both groups, optimal information size criteria not met. 95% CI may not include a meaningful difference (i.e. crossing the null value), thus treatment A failed to show or exclude a beneficial effect as compared to treatment B.
h. Attrition bias and bias related to the sources of funding were considered potentially significant.
i. Optimal information size criteria not met suggests fragility of the reported estimate.

References

1.Kaye KS, Rice LB,Dane AL,Stus V,Sagan O,Fedosiuk E,Das AF,Skarinsky D,Eckburg PB,Ellis-Grosse EJ. Fosfomycin for Injection (ZTI-01) Versus Piperacillin tazobactam for the Treatment of Complicated Urinary Tract Infection Including Acute Pyelonephritis: ZEUS, A Phase 2/3 Randomized Trial. Clinical Infectious Diseases; 2019.
2.J, Sojo-Dorado, I, López-Hernández, C, Rosso-Fernandez, IM, Morales, ZR, Palacios-Baena, A, Hernández-Torres, E, Merino,de,Lucas, L, Escolà-Vergé, E, Bereciartua, E, García-Vázquez, V, Pintado, L, Boix-Palop, C, Natera-Kindelán, L, Sorlí, N, Borrell, L, Giner-Oncina, C, Amador-Prous, E, Shaw, A, o,Jover-Saenz, J, Molina, RM, Martínez-Alvarez, CJ, Dueñas, J, Calvo-Montes, JT, Silva, MA, Cárdenes, Lecuona, M, V, Pomar, Valiente de Santis, L, G, Yagüe-Guirao, Lobo-Acosta MA, Merino-Bohórquez V, A, Pascual, Rodríguez-Baño, J and the REIPI-GEIRAS-FOREST grou. Effectiveness of Fosfomycin for the Treatment of Multidrug-Resistant Escherichia coli Bacteremic Urinary Tract Infections A Randomized Clinical Trial. JAMA Network Open; 2022.

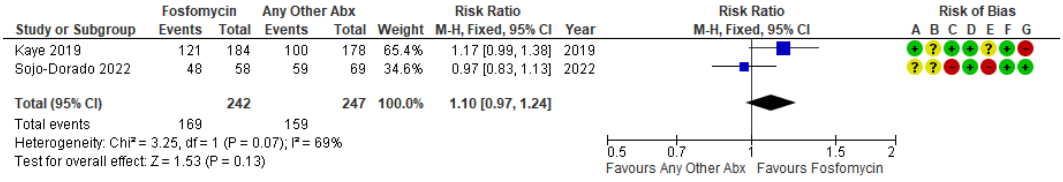
Supplementary Figures A.10: Forest plots for each patient-important outcome

A.10a) Clinical cure (at Test-Of-Cure (TOC))



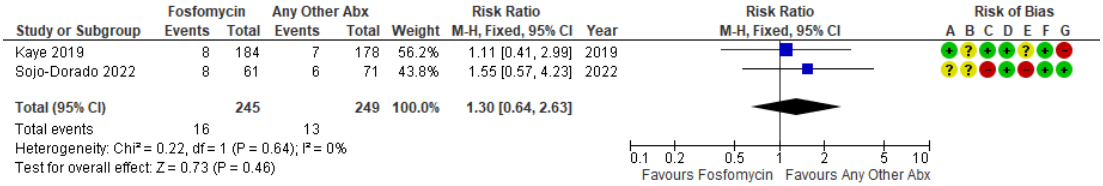
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.10b) Microbiological cure (at TOC)



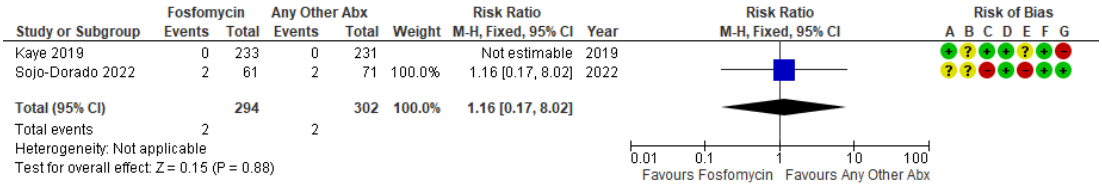
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.10c) Recurrence of Infection (at Late Follow Up (LFU))



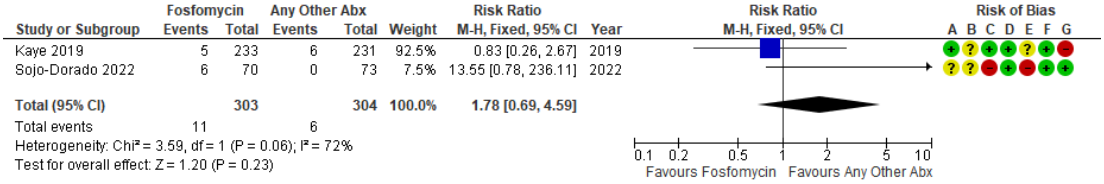
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.10d) Mortality



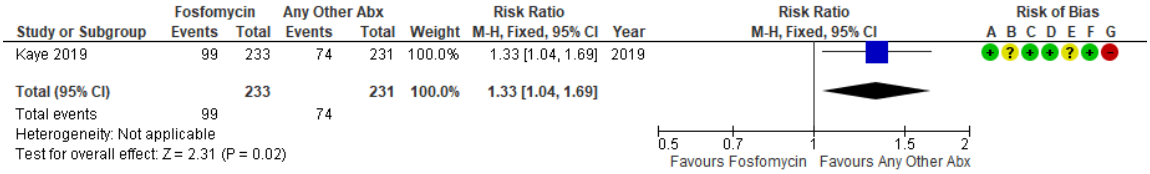
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.10e) Serious Adverse Events



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

A.10f) Non-Serious Adverse Events



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

For older aminoglycosides

Literature Search Strategies (last updated September 15th, 2024)

PubMed

1. cystitis
2. cystitis[MeSH Terms]
3. pyelonephritis
4. pyelonephritis[MeSH Terms]
5. complicat* AND "urinary tract infection*"
6. urinary tract infection[MeSH Terms]
7. 1 OR 2 OR 3 OR 4 OR 5 OR 6
8. gentamicin
9. amikacin
10. tobramycin
11. aminoglycoside*
12. 8 OR 9 OR 10 OR 11
13. 7 AND 12
14. "Epidemiologic Studies"[Mesh:NoExp]
15. "Case-Control Studies"[MeSH Terms]
16. "Cohort Studies"[MeSH Terms]
17. "Cross-Sectional Studies"[MeSH Terms]
18. "case control"[tiab] OR "cohort stud*"[tiab]
19. "cohort analy*"[tiab]
20. "follow up stud*"[tiab]
21. "observational stud*"[tiab]
22. longitudinal[tiab]
23. retrospective[tiab]
24. "cross sectional"[tiab]
25. 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24
26. 13 AND 25
27. "2008"[Date - Publication] : "3000"[Date - Publication]
28. 26 AND 27
29. "english"[Language]
30. 28 AND 29

Embase

1. 'urinary tract infection'/exp
2. 'urinary tract infection*'
3. 'urinary tract infections'/exp
4. 'cystitis'/exp
5. cystitis
6. 'pyelonephritis'/exp
7. pyelonephritis
8. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9. ‘gentamicin'/exp
10. gentamicin
11. 'amikacin'/exp
12. amikacin
13. 'tobramycin'/exp
14. tobramycin

15. 'aminoglycoside'/exp
16. aminoglycoside
17. #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
18. #8 AND #17
19. 'epidemiologic study'
20. 'case control study'
21. 'cohort analysis'
22. 'cross-sectional study'
23. 'case control':ab,ti
24. 'cohort stud*':ab,ti
25. 'cohort analy*':ab,ti
26. 'follow up stud*':ab,ti
27. 'observational stud*':ab,ti
28. longitudinal:ab,ti
29. retrospective:ab,ti
30. 'cross sectional':ab,ti
31. #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30
32. #18 AND #31
33. [english]/lim)
34. #32 AND #33
35. 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py OR 2021:py OR 2022:py OR 2023:py
36. #34 AND #35

Cochrane

1. MeSH descriptor: [Cystitis] explode all trees
2. cystitis
3. cystitides
4. MeSH descriptor: [Pyelonephritis] explode all trees
5. pyelonephritis
6. MeSH descriptor: [Urinary Tract Infections] explode all trees
7. "urinary tract infection*"
8. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9. gentamicin
10. amikacin
11. tobramycin
12. aminoglycoside*
13. #9 OR #10 OR #11 OR #12
14. #8 AND #13 with Cochrane Library publication date from Jan 2008 to present

Eligibility criteria for selection of the studies

Inclusion criteria:

- Patient population: Adults patients presenting cUTI (with or without sepsis, with or without risk of resistance)
- Intervention:
    Older aminoglycosides (parenteral): gentamicin, amikacin, tobramycin (minimally as part of the main antibiotic therapy received)

-Comparator: any direct comparison with antibiotics of interest from the initial list of included antibiotics (either parenteral or oral) (see eligibility criteria for all antibiotics except older aminoglycosides)

-Outcomes
    -Minimally including mortality (at 30 days)

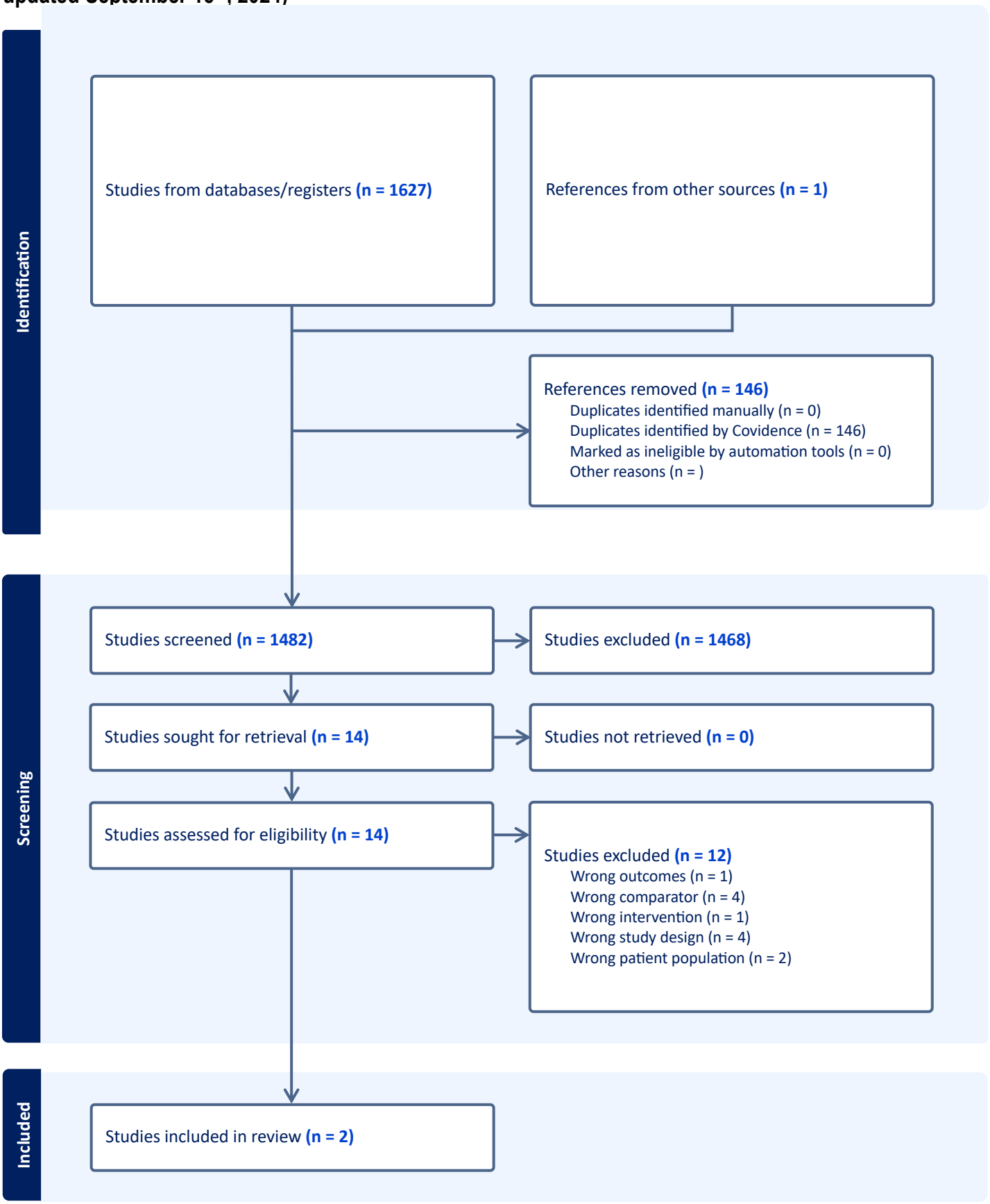
- Study design: Observational studies (i.e. cohort studies)
- Year: published from 2008 up to present
- Language: English only

Exclusion criteria:

-Patient population:
    -Children
    -Renal transplant patients
    -Neutropenic patients
    -Pregnant women and lactating women
    -Uncomplicated UTI

-Outcome
    -Not including mortality (at 30 days)

Supplementary Figure A.11: Prisma Flow Diagram of study identification and selection (last updated September 15th, 2024)



Supplementary Table A.11: Characteristics of the included studies (n=2, 2008-2024)

Study *(Lead author, Year of publication, Name of trial, Countries)*	**Population** *(Type UTI, Year of enrollment, n randomised, F (%), Age)*	**Study design** *(Non-inferiority margin if applicable, primary outcome with its timing)*	**Main uro-pathogens**	**Intervention** *(Antibiotic(s), % of resistance)*	**Comparator** *(Antibiotic(s), % of resistance)*	**Duration and Route of administration**
Elbaz 2020 Israel (single center)	AP, only hospitalized patients, empiric Tx 2017-2019 N=2026 (715 aminos vs 1311 non-aminos) F: 56% Age: 82y	Retrospective cohort study 30-day mortality (propensity score adjusted)	*E. coli* (58%) ESBL (31%)	Aminoglycoside-based regimen (gentamicin or amikacin, with or without the addition of ampicillin) R: 8.5% (61/715)	Non-aminoglycoside regimen (ceftriaxone, piperacillin-tazobactam, carbapenems) R : 19.9% (261/131)	IV: received for median 4 days Total duration: 5 days
Zohar 2020 Israel (single center)	Bacteremic UTI/AP or urosepsis, only in ESBL-Enterobacteriaceae 2014-2017 N=218 (108 aminos vs 95 non-aminos) F: 47% Age: 79y	Retrospective cohort study 30-day mortality (logistic regression)	*E. coli* (61%) ESBL (100%)	Aminoglycoside (amikacin and gentamicin) R: NR but assumed 0% since definitive Tx	Carbapenems (mostly ertapenem) or piperacillin-tazobactam) R: NR but assumed 0% since definitive Tx	Total duration: 8 days
UTI: Urinary Tract Infection; AP: acute pyelonephritis; N: number; F: female, y: years; NR: not reported; Tx: therapy R: resistant, including non-susceptible; S: susceptible; ESBL: Extended Spectrum Beta-Lactamase; IV: parenteral						

Supplementary Table A.12: Assessment of the Risk of bias of included studies (ROBINS-I tool)

Studies	Overall Risk of bias	Confounding	Selection of participants into the study	Classification of interventions	Deviation from intended interventions	Missing data	Measurement of outcomes	Selection of the reported result
Elbaz 2020	**Critical**	Serious residual confounding (adjustment restricted to propensity score, which included only 3 variables)	Confounding-by-indication (propensity-score adjustment)	Intervention status clearly defined, but minimal duration of intervention not reported	No information on co-intervention initially used (i.e. ampicillin) or switch to if initial EAT was inappropriate (i.e. resistance)	No information on missing data or potential for data to be missing	Outcome assessments were comparable between groups and unlikely to be influenced by the knowledge of the intervention for objective outcomes (e.g. mortality) but it remains unclear if monitory of AKI was similar in both groups.	The outcome measurement and analyses are consistent except for defervescence that was defined as a binomial variable and reported as a continuous variable
Zohar 2020	**Critical**	Serious residual confounding (multivariate analysis included 4 variables)	Confounding-by-indication with evidence of residual confounding (no adjustment)	Intervention status and minimal duration clearly defined	Deviation from the intended intervention was described (treatment switch) but no analysis provided to estimate the effect of deviation on outcomes	Missing data reported (e.g. recurrence bacteriuria within 90 days) but the no information provided on differences between interventions or if/how it was addressed in the analysis	Outcome assessments were comparable between groups and unlikely to be influenced by the knowledge of the intervention for objective outcomes (e.g. mortality) but it remains unclear if monitory of AKI was similar in both groups.	The outcome measurement and analyses are consistent

ROBINS-I : Risk of bias In Non-Randomised Studies of Interventions; **EAT:** empiric antibiotic therapy

Risk of bias judgement

Low	
Moderate	
Serious	
Critical	
No information	

Older aminoglycosides

Supplementary Table A.13: GRADE Evidence Profile

Question: In patients presenting with complicated UTI, should **older aminoglycosides** be used rather than **Any Other Abx** for empirical therapy?

P: In patients with complicated UTI
I: Older aminoglycosides for empirical therapy
C: Any Other Abx for empirical therapy
Setting: Inpatient and Outpatient

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Old Aminoglycosides	Any Other Abx *	Relative (95% CI)	Absolute (95% CI) &		
Mortality (at 30 days)												
2[1,2]	NRS	serious[a]	not serious	not serious	not serious	none	55/715 (7.7%)	145/1311 (11.1%)	**aRR 0.78** (0.65 to 0.95)	**24 fewer per 1,000** (from 39 fewer to 6 fewer)	⊕◯◯◯ Very low	CRITICAL
							14/108 (13.0%)	18/85 (21.2%)	**aOR 0.51** (0.24 to 1.06)	**103 fewer per 1,000** (from 214 fewer to 8 more)		
Microbiological cure (90 days)												
1[2]	NRS	very serious[b]	not serious	serious[c]	very serious[d]	none	23/45 (51.1%)	21/38 (55.3%)	**aOR 0.70** (0.28 to 1.72)	**89 fewer per 1,000** (from 294 fewer to 128 more)	⊕◯◯◯ Very low	IMPORTANT
Acute Renal Injury												
1[1,2]	NRS	serious[a]	not serious	not serious	serious[e]	none	18/715 (2.5%)	39/1311 (3.0%)	**aRR 0.98** (0.97 to 1.004)	**1 fewer per 1,000** (from 1 fewer to 0 fewer)	⊕◯◯◯ Very low	IMPORTANT
							20/108 (18.5%)	9/85 (10.6%)	**OR 1.14** (0.46 to 2.81)	**13 more per 1,000** (from 54 fewer to 144 more)		
Rehospitalisation (at 3 months)												
1[1]	NRS	serious[a]	not serious	not serious	not serious	none	181/715 (25.3%)	418/1311 (31.9%)	**aRR 0.95** (0.91 to 0.99)	**16 fewer per 1,000** (from 29 fewer to 3 fewer)	⊕◯◯◯ Very low	IMPORTANT
Length of hospital stay												
1[1]	NRS	serious[a]	not serious	not serious	not serious	none	5	6	-	**aMD 2.5 days fewer** (3.6 fewer to 1.4 fewer)	⊕◯◯◯ Very low	IMPORTANT

***Any other antibiotics:** Non-aminoglycosides regimens (ceftriaxone, piperacillin-tazobactam or carbapenems) (Elbaz 2020) and carbapenem (mainly ertapenem) or piperacillin-tazobactam (Zohar 2020)
****Resistance rate at baseline (in analyzed populations) reported only in Elbaz 2020:** 8.6% in the aminoglycoside group versus 20% in the non-aminoglycoside comparator group.
*****Clinical cure, Progression of infection, and recurrence of infection were not reported (important PIOs).**
[&]**Visual Interpretation of 95% Confidence Interval boundaries for the Absolute Effect**: if the lower boundary of the 95% CI is **highlighted in red,** it means it is crossing the non-inferiority margin of 10% (below 100 fewer per 1,000 patients = non-inferior), and if one boundary of the 95% is **highlighted in blue,** it means that it is not crossing the null value for superiority (i.e. confidence interval not including zero = superior or inferior).

NRS: Non-Randomised Studies; **CI:** confidence interval; **Abx:** antibiotics; a**MD:** adjusted mean difference; a**OR:** adjusted odds ratio; **OR:** odds ratio; a**RR:** adjusted risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Old Aminoglycosides	Any Other Abx *	Relative (95% CI)	Absolute (95% CI) &		

GRADE domains

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

Explanations

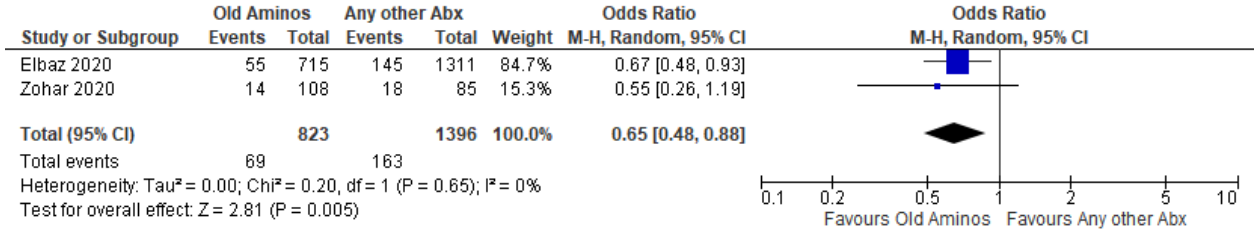
a. Confounding by indication with evidence of residual confounding and lack of blinding were considered significant.
b. Confounding by indication with evidence of residual confounding, lack of blinding and attrition bias were considered significant.
c. Microbiological cure is considered to be potential surrogate marker of clinical cure and recurrence of infection, but uncertainty remains around the strength of this association.
d. Small number of events and sample size with very wide confidence interval.
e. 95% CI may not include a meaningful difference (i.e. crossing the null value), thus treatment A failed to show or exclude undesirable effect as compared to treatment B.

References

1. Elbaz M, Zadka H,Weiss-Meilik A,Ben-Ami R. Effectiveness and safety of an institutional aminoglycoside-based regimen as empirical treatment of patients with pyelonephritis. J Antimicrob Chemother; 2020.
2.Zohar I, Schwartz O,Yossepowitch O,Shapiro Ben David S,Maor Y. Aminoglycoside versus carbapenem or piperacillin/tazobactam treatment for bloodstream infections of urinary source caused by Gram-negative ESBL-producing Enterobacteriaceae. J Antimicrob Chemother; 2020

Supplementary Figure A.12: Forest plot for 30-day mortality

30-day Mortality (unadjusted analysis)



B. Stepwise Process to Guide Empiric Antibiotic Choice

Step 1: Severity of illness / Impact of Inappropriate Empiric Antibiotic Therapy in complicated UTI

Literature Search Strategies (last updated September 2nd, 2023)

Medline (PubMed)

1. cystitis
2. pyelonephritis
3. "urinary tract infection"
4. "urinary tract infections"
5. "Urinary Tract Infections"[MeSH Terms]
6. cystitis[MeSH Terms]
7. pyelonephritis[MeSH Terms]
8. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
9. empiric*
10. initial
11. 9 OR 10
12. antibiotic*
13. antimicrobial
14. treatment*
15. therap*
16. 12 OR 13 OR 14 OR 15
17. 11 AND 16
18. inappropriate
19. delayed
20. discordant
21. inadequate
22. incorrect
23. ineffective
24. 17 OR 18 OR 19 OR 20 OR 21
25. 8 AND 17 AND 24
26. editorial[Publication Type]) OR (letter[Publication Type]) OR (news[Publication Type]) OR (newspaper article[Publication Type]) OR (congress[Publication Type] OR "case reports"[Publication Type]
27. 25 NOT 26
28. "2000"[Date - Publication] : "3000"[Date - Publication]
29. 27 AND 28
30. "english"[Language]
31. 29 AND 30
32. (animal OR animals OR canine* OR dog OR dogs OR feline OR hamster* OR lamb OR lambs OR mice OR monkey OR monkeys OR mouse OR murine OR pig OR pigs OR piglet* OR porcupine OR primate* OR rabbit* OR rats OR rat OR rodent* OR sheep*) NOT (human* OR patient*)
33. 31 NOT 32

EMBASE

1. cystitis
2. 'cystitis'/exp
3. pyelonephritis
4. 'pyelonephritis'/exp
5. ‘urinary tract infection'/exp
6. ‘urinary tract infections'
7. ‘urinary tract infection’

8. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
9. 'antiinfective agent'/exp
10. antibiotic*
11. antimicobial*
12. treatment
13. therap*
14. 9 OR 10 OR 11 OR 12 OR 13
15. empiric*
16. initial
17. 15 OR 16
18. 14 AND 17
19. inappropriate
20. delayed
21. discordant
22. inadequate
23. incorrect
24. ineffective
25. 19 OR 20 OR 21 OR 22 OR 23 OR 24
26. 8 AND 18 AND 25
27. editorial:it OR letter:it OR news:it OR newspaper:it OR conference*:it
28. 26 NOT 27
29. [english]/lim
30. 28 AND 29
31. [humans]/lim
32. 30 AND 31
33. [2000-2023]/py
34. 32 AND 33

Cochrane Library

1. MeSH descriptor: [Cystitis] explode all trees
2. cystitis
3. MeSH descriptor: [Pyelonephritis] explode all trees
4. pyelonephritis
5. "urinary tract infection"
6. "urinary tract infections"
7. MeSH descriptor: [Urinary Tract Infections] explode all trees
8. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9. (empiric* OR initial) NEAR5 (antibiotic* OR antimicrobial OR treatment* OR therap*)
10. (inappropriate OR delayed OR discordant OR inadequate OR incorrect OR ineffective)
11. #9 AND #10
12. #8 AND #11 with Cochrane Library publication date from Jan 2000 to present

Eligibility criteria for selection of the studies

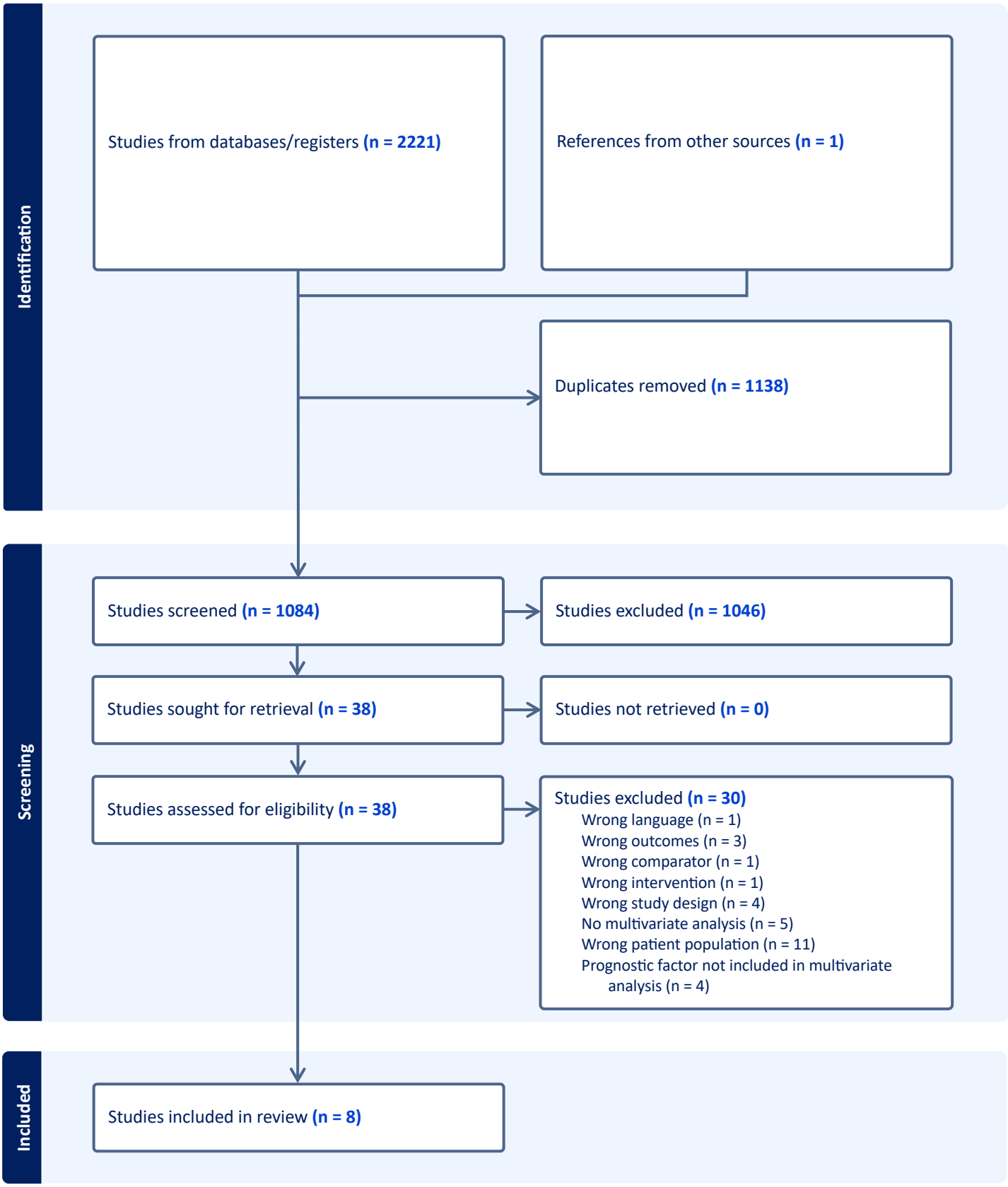
Inclusion criteria:

- Patient population: Adults patients presenting cUTI (with or without sepsis, with or without risk of resistance)
- Prognostic factor:
  - -Inappropriate empiric antimicrobial therapy (based on the results of the urine culture in vitro susceptibility testing of the causative organisms)
    vs
  - - Appropriate empiric antimicrobial therapy (based on the results of the urine culture in vitro susceptibility testing of the causative organisms)
- -Outcomes
  - -Mortality (all-cause at 30 days or in-hospital)
  - -Clinical cure
- - Study design: Observational studies (i.e. cohort studies), presenting a multivariate analysis for the outcome(s) of interest
- - Year: published from 2000 up to present
- - Language: English only

Exclusion criteria:

- -Patient population:
  - -Children
  - -Renal transplant patients
  - -Neutropenic patients
  - -Pregnant women and lactating women
  - -Uncomplicated UTI
- -Outcome
  - -Not including mortality (at 30 days) or clinical cure

Supplementary Figure B1.a: Prisma Flow Diagram of study identification and selection (last update September 2nd, 2023)



Supplementary Table B1.a: Characteristics of the included studies for impact of Inappropriate Empiric on mortality (n=8, 2000-2023)

Study *(Lead author, Year of publication, Countries)*	**Population** *(Type UTI, Year of enrollment, n included, F (%), Age)*	**Study design** *(outcome of interest, with its timing)*	**Prevalence of IEAT* (***% and explanation, if provided***)**	**Severity of disease at clinical presentation**	**Baseline mortality** (in patients receiving AEAT)	**Other variable included in the multivariate analysis**
Babich 2017 Israel (one center)	Hospitalized **CA-UTI** with sepsis 2010-2015 N=315 F: 43% Age: 79y	Prospective cohort 30-day all cause mortality	50.%	-Bacteremia: 24% -Vasopressor support: 10%	32.9%	Age, malignancy, heart failure, nasogastric tube, SOFA score, central line, and functional capacity-depended/bedridden + Adjustment with a propensity score matching for AEAT
Esparcia 2014 Spain (one center)	Hospitalized non-ICU UTI 2009-2012 N=270 F:60% Age: 84y	Retrospective cross-sectional In-hospital mortality	29.3% (due to quinolone-resistant *E. coli* treated with a fluoroquinolone or *Enterococcus faecalis* with a cephalosporin)	-Bacteremia: 21% -APACHE ≥15: 41% -Severe sepsis and septic shock: 26%	5.8%	APACHE more or equal to 15, dementia, and solid neoplasia
Holmbom 2022 Sweden (one county)	Hospitalized **bacteremic UTI** 2019-2020 N=282 F: 42% Age: 72y	Retrospective cohort 30-day mortality	10.3%	-Bacteremia: 100% -Sepsis: 92% -ICU admission: 20%	11.5%	Male, age, Charlson score, In-SOFA, SOFA score at 24h, CT-scan or ultrasound during the hospital episode, and urinary tract disorder
Korkmaz 2020 Turkey (33 centers)	Hospitalized UTI 2017 N=525 F: 52% Age: 77y	Not reported (likely retrospective cohort) In-hospital mortality	29.7% (due to ESBL Gram-negative uropathogens treated with ceftriaxone)	-Bacteremia: 15% -Sepsis: 24% -Septic shock: 3%	7.3%	Age, site of admission, dx (pyelonephritis, urosepsis, septic shock), temporary urinary catheter, ICU, comorbidities, vital signs, and BUN
Ortega 2013 Spain (one center)	Hospitalized **bacteremic CA-UTI** 1991-2010 N=1007 F: 26% Age: 69y	Prospective cohort Attributable mortality	17.3%	Septic shock: 12%	7.2%	Ultimately or rapidly fatal prognosis of underlying disease and shock on presentation
Righolt 2020 Canada (one province)	Hospitalized cUTI 2006-2014 N=792 F: 62% Age: 41% over 76y	Retrospective cohort 30-day mortality	11.1%	ICU admission: 21%	6.1%	Gender, age 65+, rural residence, chronic condition as comorbidity, hospitalization in the previous year, and living in long-term care
Rodriguez-Gomez 2019 Spain	Hospitalized KPC-Kp UTI 2012-2015 N=142	Retrospective cohort All-cause mortality	50.0%	-Bacteremia: 15% -Septic shock: 17%	33.3%	Gender, Charlson morbidity index, and Pitt bacteremia score

(one center)	F: 43% Age: 78y					
Wiggers 2019 Canada (one center)	Hospitalized **bacteremic UTI** 2010-2015 N=469 F: 54% Age: 72y	Retrospective cohort 30-day mortality	21.5%	-Bacteremia: 100% -qSOFA > 1: 44% -ICU admission: 16%	9.5%	Unclear

UTI: Urinary Tract Infection; **CA-UTI:** Catheter Associated UTI; **KPC-Kp:** *Klebsiella pneumoniae* Carbapenemase – *Klebsiella pneumoniae*; ESBL: Extended Spectrum Beta-Lactamase; N: number; F: female, y: years; NR: not reported

IEAT (Inappropriate Empiric Antimicrobial Therapy): mismatched between urine culture in vitro susceptibility testing of the causative organisms and the antibiotics initially received at clinical presentation; **AEAT** (Appropriate Empiric Antimicrobial Therapy): matched between urine culture in vitro susceptibility testing of the causative organisms and the antibiotics initially received at clinical presentation.

ICU: Intensive care unit; BUN: Blood Urea Nitrogen; APACHE: Acute Physiology and Chronic Heath Evaluation; SOFA: Sequential Organ Failure Assessment; qSOFA: quick Sepsis-related Organ Failyre Assessment.

Supplementary Table B1.b: Summary of the Risk of bias of the included studies (QUIPS tool)

	Overall Risk of bias	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Babich 2017	Low	Low	Low	Low	Low	Low	Low
Esparcia 2014	High	Low	Low	Low	Moderate	High	High
Holmbom 2022	Moderate	Moderate	Low	Low	Low	Moderate	Moderate
Korkmaz 2020	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
Ortega 2013	Moderate	Moderate	Low	Low	Low	Moderate	Moderate
Righolt 2020	High	High	Low	Low	Low	Moderate	Moderate
Rodriguez-Gomez 2019	Moderate	Moderate	Low	Low	Low	Moderate	Moderate
Wiggers 2019	Moderate	Moderate	Low	Low	Low	Moderate	Moderate

QUIPS: Quality in Prognostic Studies

Risk of bias judgement

Low	
Moderate	
High	

Study design and risk of bias (narrative explanation)

Although the overall risk of bias among these was judged as moderate according to the QUIPS Risk of Bias Tool, we urge caution in interpretating these results. All these studies were observational, and all but one (Babich 2017) were retrospective. Clinicians' initial choice of empiric antibiotic therapy introduced confounding by indication, which was either partially or not accounted for at all in most studies. For example, patients with sepsis are more likely to receive broader spectrum antibiotics (potentially providing a higher rate of appropriate empiric antibiotic therapy, or AEAT) but are also more likely to die. In this case, one may falsely conclude that receiving AEAT increases the risk of mortality (or that IEAT is associated with a lower risk of mortality). Conversely, clinicians might give broader spectrum antibiotics to patients who are younger and more likely to survive, creating the false impression that AEAT decreases risk of mortality.

Another challenge to the validity of the findings is that some small sample sizes resulted in imbalances between the groups, contributing residual confounding. In the Esparcia et al. cohort (Esparcia 2014), 41% of the IEAT group had an indwelling urinary catheter, while only 26% of the AEAT group had indwelling urinary catheter. They reported that IEAT was an independent risk factor for mortality, but clearly the two groups were not matched. As another example, having a Gram-positive organism (*Enterococcus faecalis*) as the cause of bacteremic cUTI was a risk factor for mortality in Holmbom 2022, but this may be confounded as having enterococcus as the organism was associated with IEAT in several studies (Esparcia 2014, Ortega 2013, Wiggers 2019).

Whether or not these findings are generalizable to the entire cUTI population is a concern, as three of these studies only included cUTI patients who were also bacteremic, and these three studies accounted for 46% of the total patients (Holmbom 2022, Ortega 2013, Wiggers 2019). Another major concern is uncertainty in the diagnosis of cUTI. One of these studies (accounting for 792 or 21% of the patients) was entirely a database study without any individual chart review (Righolt 2020). As the authors note, their retrospective analysis of patients admitted to the hospital and with a positive urine culture could not distinguish between patients with cUTI and those with asymptomatic bacteriuria (ASB), thus diluting the impact of IEAT. This same issue arises in other studies; in patients with sepsis and positive urine culture, the urinary organism may not be the cause of the sepsis, unless also identified in the bloodstream.

Impact of Inappropriate Empiric Antimicrobial Therapy

Supplementary Table B1.c: GRADE Evidence Profile

Question: What is the prognostic impact of inappropriate empiric antimicrobial therapy in the treatment of complicated UTI?

P: In patients with complicated UTI
I: Inappropriate empiric antimicrobial therapy
C: Appropriate empiric antimicrobial therapy
Setting: Inpatient and Outpatient

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IEAT	AEAT	Adjusted relative risk (95% CI)	Absolute (95% CI)		
Mortality (in-hospital or at 30 days)												
7[1,2,3,4,5,6,8]	observational studies	serious[a]	serious[b]	not serious	not serious[c]	reporting bias[d]	371 deaths and 3080 survivals in the initial cohort = 10.8% mortality rate (9.0% baseline mortality rate (in AEAT group)) **Cohorts with IEAT ranging from 10-50%**		**aOR 1.56** (0.99 to 2.46)	- **51 more per 1,000** (from 1 fewer to 121 more) **5.1 more deaths per 100 patients (from 0.1 less deaths to 12.1 more deaths) with IEAT**	⊕◯◯◯ Very low	CRTICAL
1[7]	observational study						46 deaths and 96 survivals in the initial cohort = 32.4% mortality rate (33.8% baseline mortality rate (in AEAT group) **Cohort with IEAT 21.5%**		**aHR 1.99** (0.94 to 4.21)	-		

Notes:
IEAT (Inappropriate Empiric Antimicrobial Therapy): mismatched between urine culture in vitro susceptibility testing of the causative organisms and the antibiotics initially received at clinical presentation
AEAT (Appropriate Empiric Antimicrobial Therapy): matched between urine culture in vitro susceptibility testing of the causative organisms and the antibiotics initially received at clinical presentation.
***Clinical cure was not reported or not adjusted for other confounders (critical PIOs).**

CI: confidence interval; **aOR**: adjusted odds ratio; **aHR:** adjusted hazard ratio.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

GRADE domains
Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

Explanations

a. Moderate Risk of bias (QUIPS) mainly due to confounding-by-indication and likely residual confounding
b. Clinical and Statistical heterogeneity: p-value 0.002, I-square: 72% (heterogeneity not explained by baseline mortality and rate of IEAT)
c.. Crossing the null value, but very likely due to heterogeneity (thus not rated down)
d. Potential of overestimating the effect due to potential reporting bias of non-statistically significant ORs in studies that could not be included in our analysis

References

1. Babich T, Zusman O, Elbaz M, Ben-Zvi H, Paul M, Leibovici L, Avni T. Empirical Antibiotic Treatment Does Not Improve Outcomes in Catheter-Associated Urinary Tract Infection: Prospective Cohort Study. Clin Infect Dis. 2017 Nov 13;65(11):1799-1805.
2. Esparcia A, Artero A, Eiros JM, Balaguer M, Madrazo M, Alberola J, Nogueira JM. Influence of inadequate antimicrobial therapy on prognosis in elderly patients with severe urinary tract infections. Eur J Intern Med. 2014 Jul;25(6):523-7.
3. Holmbom M, Andersson M, Grabe M, Peeker R, Saudi A, Styrke J, Aljabery F. Community-onset urosepsis: incidence and risk factors for 30-day mortality - a retrospective cohort study. Scand J Urol. 2022 Oct-Dec;56(5-6):414-420.
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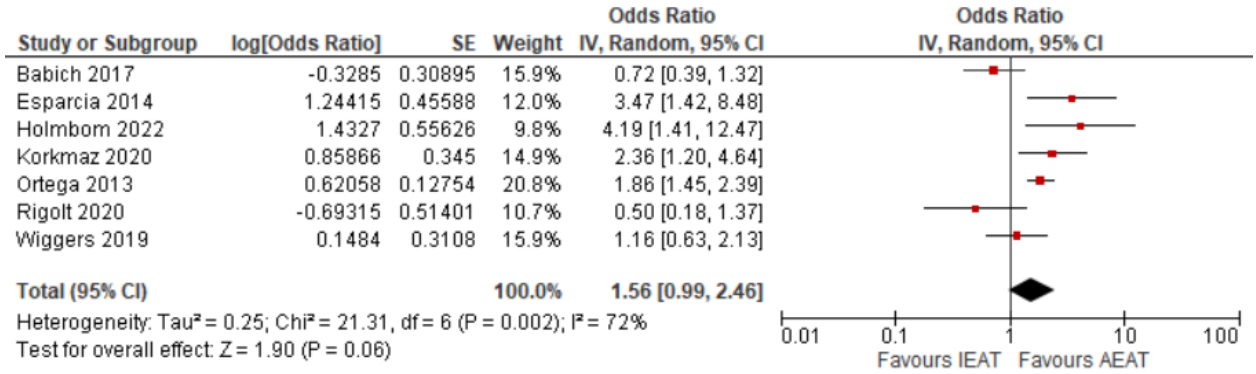
7. Rodriguez-Gómez J, Pérez-Nadales E, Gutiérrez-Gutiérrez B, Machuca I, Martinez-Martinez L, Rivera F, Cano A, Castón JJ, Robles JC, de la Fuente C, Rodríguez-López F, Rodriguez-Baño J, Torre-Cisneros J. Prognosis of urinary tract infection caused by KPC-producing Klebsiella pneumoniae: The impact of inappropriate empirical treatment, Journal of Infection, 2019, 79 (3): 245-252.
8. Wiggers JB, Sehgal P, Pinto R, MacFadden D, Daneman N. The association of adequate empirical treatment and time to recovery from bacteraemic urinary tract infections: a retrospective cohort study. Clin Microbiol Infect. 2019 Oct;25(10):1253-1258.

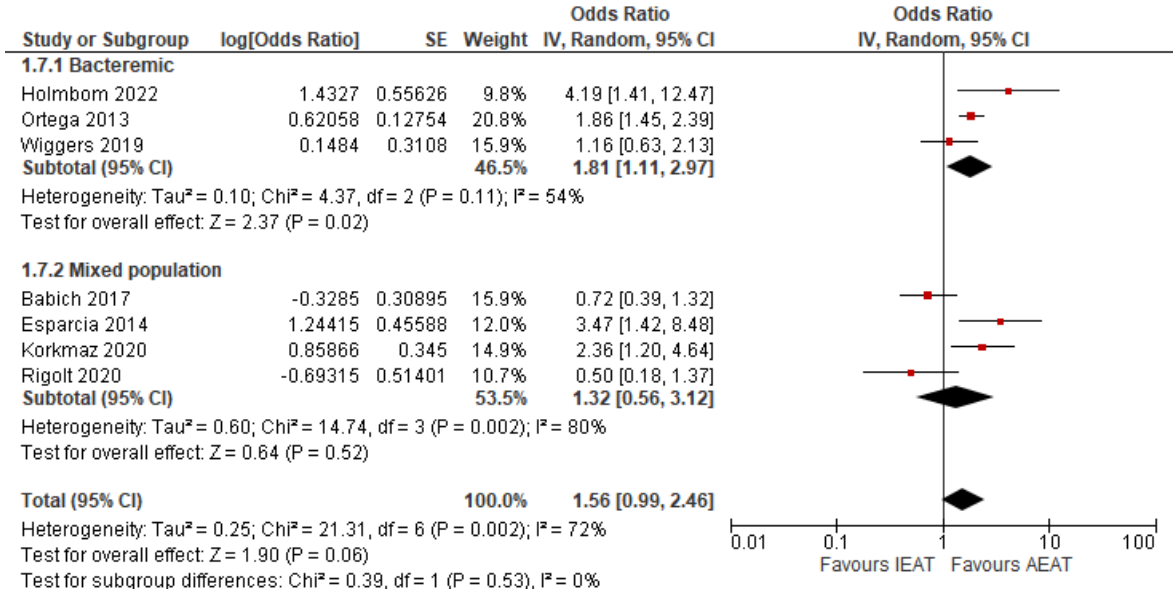
Supplementary Figures B1.b: Forest Plots for mortality

B1.b) Mortality (adjusted Odds Ratio)

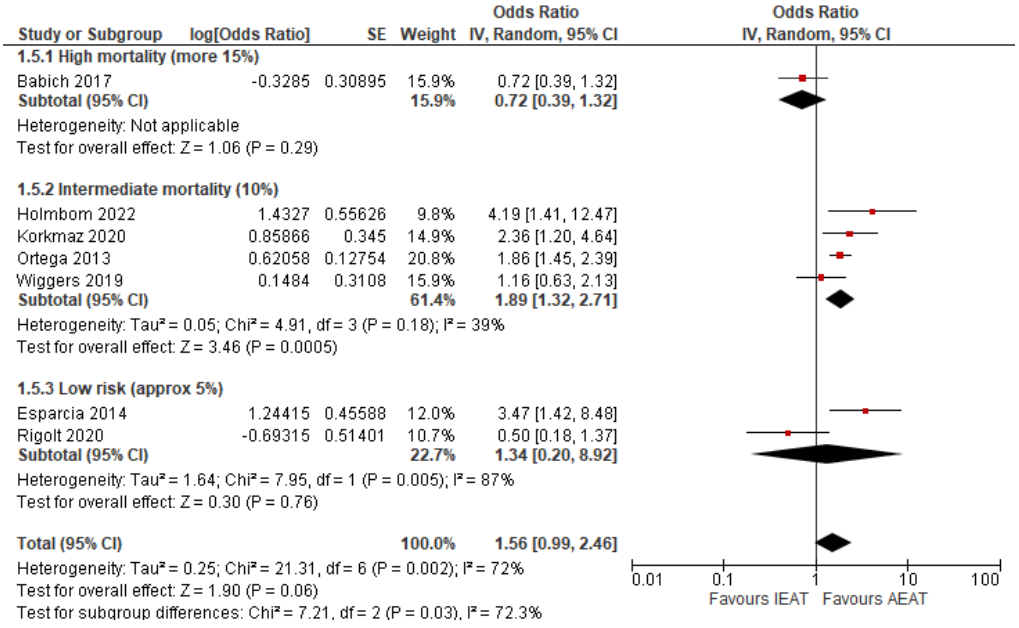


Subgroup analysis (heterogeneity)

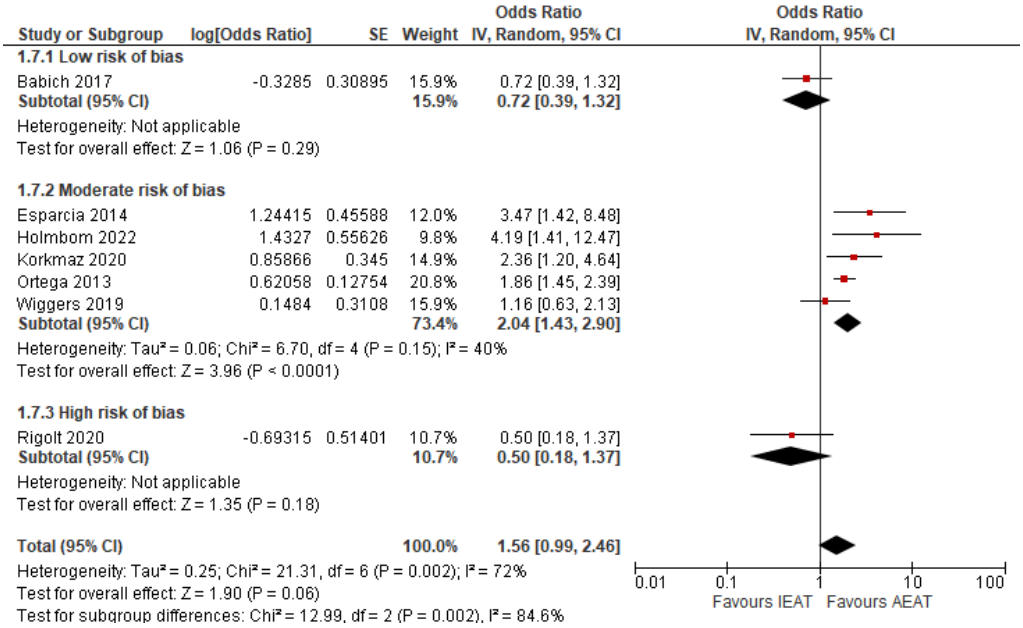
1. Stratified by bacteremic population vs mixed population



2. Stratified by baseline mortality (in the appropriate empiric antimicroabila therapy (AEAT) group)



3. Stratified by risk of bias (Low, Moderate, High risk of bias according to QUIPS)



Step 2: Patient-specific risk factors for resistant uropathogens

Methods (general concepts)

After acknowledging the importance of inappropriate empiric antibiotic therapy on mortality in patients with sepsis and potential for clinical failure, we aimed at identifying patient-specific risk factors that could help optimize the choice of empiric antibiotics. To capture all variables that could potentially influence the decision-making process, a comprehensive search strategy was developed using a combination of database-specific subject headings and text words for the two main concepts: 1) improvement of appropriateness of empiric antibiotic therapy in patients with UTI, and 2) risk factors that the patient would have an antibiotic-resistant uropathogen. These two search strategies were designed to be very sensitive with very low specificity and were expected to provide overlapping results.

We included studies that been published between 2000 and present (2023), from any geographic location, including patients presenting with any type of UTI. Excluded populations were renal transplant patients, neutropenic patients, children and pregnant women and lactating women. Please refer to the Methods of each subsection for the specific inclusion/ exclusion criteria used to answer each sub question within this initial database.

All following steps were performed independently and in duplicate and disagreements between authors by discussion and, if needed, via a third author. Search results were screened using Covidence software. Data extraction included information on participant characteristics, description of the risk factors, confounders, and outcomes. The risk of bias in the included studies was assessed using the Quality in Prognosis Study (QUIPS) tool. For each risk factor, we used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to appraise the certainty.

Risk estimates and associated 95% confidence intervals from individual studies were combined using the generic inverse variance method, which assigned each study's weight based on its variance. A random-effects model was used in this study. The heterogeneity of effect size estimates across the studies was quantified using the *Q* statistic and *I*2 test. A value of *I*2 of 0%–25% indicates insignificant heterogeneity, 26%–50% indicates low heterogeneity, 51%–75% indicates moderate heterogeneity, and >75% indicates high heterogeneity. Publication bias was assessed by funnel plot if an adequate number of studies were obtained. Data analysis was performed by Review Manager 5.3 software from the Cochrane Collaboration (London, UK).

Literature Search Strategy (last updated September 1st, 2023)

Improvement of appropriateness of Empiric Antibiotic Therapy

Medline (PubMed)

1. cystitis
2. pyelonephritis
3. "urinary tract infection" OR "urinary tract infections"
4. urinary tract infection[MeSH Terms]
5. cystitis[MeSH Terms]
6. pyelonephritis[MeSH Terms]
7. 1 OR 2 OR 3 OR 4 OR 5 OR 6
8. empiric*
9. Anti-Bacterial Agents [MeSH]
10. antibiotic* OR antimicrobial* OR antibacterial*
11. 9 OR 10
12. 8 AND 11
13. "initial antibiotic therapy"
14. 8 OR 13
15. match OR mismatch
16. accuracy OR accurate
17. concordance OR concordant
18. appropriate*
19. adequa*
20. perform* OR outperform*
21. maximiz* OR optim*
22. 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21
23. 14 AND 22
24. 7 AND 23
25. editorial[Publication Type] OR (letter[Publication Type]) OR (news[Publication Type]) OR (newspaper article[Publication Type]) OR congress[Publication Type] OR "case reports"[Publication Type] OR “case report*”
26. 24 NOT 25
27. "2000"[Date - Publication] : "3000"[Date - Publication]
28. 26 AND 27
29. "english"[Language]
30. 28 AND 29
31. (animal OR animals OR canine* OR dog OR dogs OR feline OR hamster* OR lamb OR lambs OR mice OR monkey OR monkeys OR mouse OR murine OR pig OR pigs OR piglet* OR porcupine OR primate* OR rabbit* OR rats OR rat OR rodent* OR sheep*) NOT (human* OR patient*)
32. 30 NOT 31

Embase

1. 'cystitis'/exp OR cystitis
2. 'pyelonephritis'/exp OR pyelonephritis
3. 'urinary tract infection'/exp OR 'urinary tract infection' OR 'urinary tract infections'
4. 1 OR 2 OR 3
5. empiric*
6. 'antiinfective agent'/exp OR antibiotic* OR antimicrobial* OR antibacterial*
7. 5 AND 6
8. 'initial antibiotic therapy'
9. 7 OR 8
10. match OR mismatch OR accuracy OR accurate OR concordance OR concordant OR appropriate* OR adequa* OR perform* OR outperform* OR maximiz* OR optim*
11. 9 AND 10
12. 4 AND 11
13. editorial:it OR letter:it OR news:it OR newspaper:it OR conference:it
14. 12 NOT 13

15. english:la
16. 14 AND 15
17. 2000:py OR 2001:py OR 2002:py OR 2003:py OR 2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py OR 2021:p
18. 16 AND 17
19. (animal OR animals OR canine* OR dog OR dogs OR feline OR hamster* OR lamb OR lambs OR mice OR monkey OR monkeys OR mouse OR murine OR pig OR pigs OR piglet* OR porcupine OR primate* OR rabbit* OR rats OR rat OR rodent* OR sheep*) NOT (human* OR patient*)
20. 18 NOT 19

Cochrane

1. cystitis
2. MeSH descriptor: [Cystitis] explode all trees
3. pyelonephritis
4. MeSH descriptor: [Pyelonephritis] explode all trees
5. urinary tract infection*
6. MeSH descriptor: [Urinary Tract Infections] explode all trees
7. #1 OR #2 OR #3 OR #4 OR #5 OR #6
8. empiric*
9. MeSH descriptor: [Anti-Bacterial Agents] explode all trees
10. antibiotic* OR antimicrobial* OR antibacterial*
11. #9 OR #10
12. #8 AND #11
13. match OR mismatch OR accuracy OR accurate OR concordance OR concordant OR appropriate* OR adequa* OR perform* OR outperform* OR maximiz* OR optim*
14. #12 AND #13
15. #7 AND #14

Risk factors for resistant uropathogens

Medline (PubMed)

1. urinary tract infection[MeSH Terms]
2. "urinary tract infection" OR "urinary tract infections"
3. cystitis[MeSH Terms]
4. cystitis
5. pyelonephritis[MeSH Terms]
6. pyelonephritis
7. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
8. prognosis[MeSH Terms]
9. prognos*[tiab]
10. risk factors[MeSH Terms]
11. risk
12. 8 OR 9 OR 10 OR 11
13. "antibiotic resistance" OR "antibiotic resistant"
14. "bacterial resistance" OR "bacterial resistant"
15. "antimicrobial stewardship" OR "antimicrobial resistance" OR "antimicrobial resistant"
16. antibacterial drug resistance[MeSH Terms]
17. drug resistance, bacterial[MeSH Terms]
18. 13 OR 14 OR 15 OR 16 OR 17 OR 18
19. 7 AND 12 AND 18
20. (editorial[Publication Type]) OR (letter[Publication Type]) OR (news[Publication Type]) OR (newspaper article[Publication Type]) OR (congress[Publication Type])
21. 19 NOT 20
22. "2000"[Date - Publication] : "3000"[Date - Publication]
23. "english"[Language]

24. 21 AND 22 AND 23

Embase

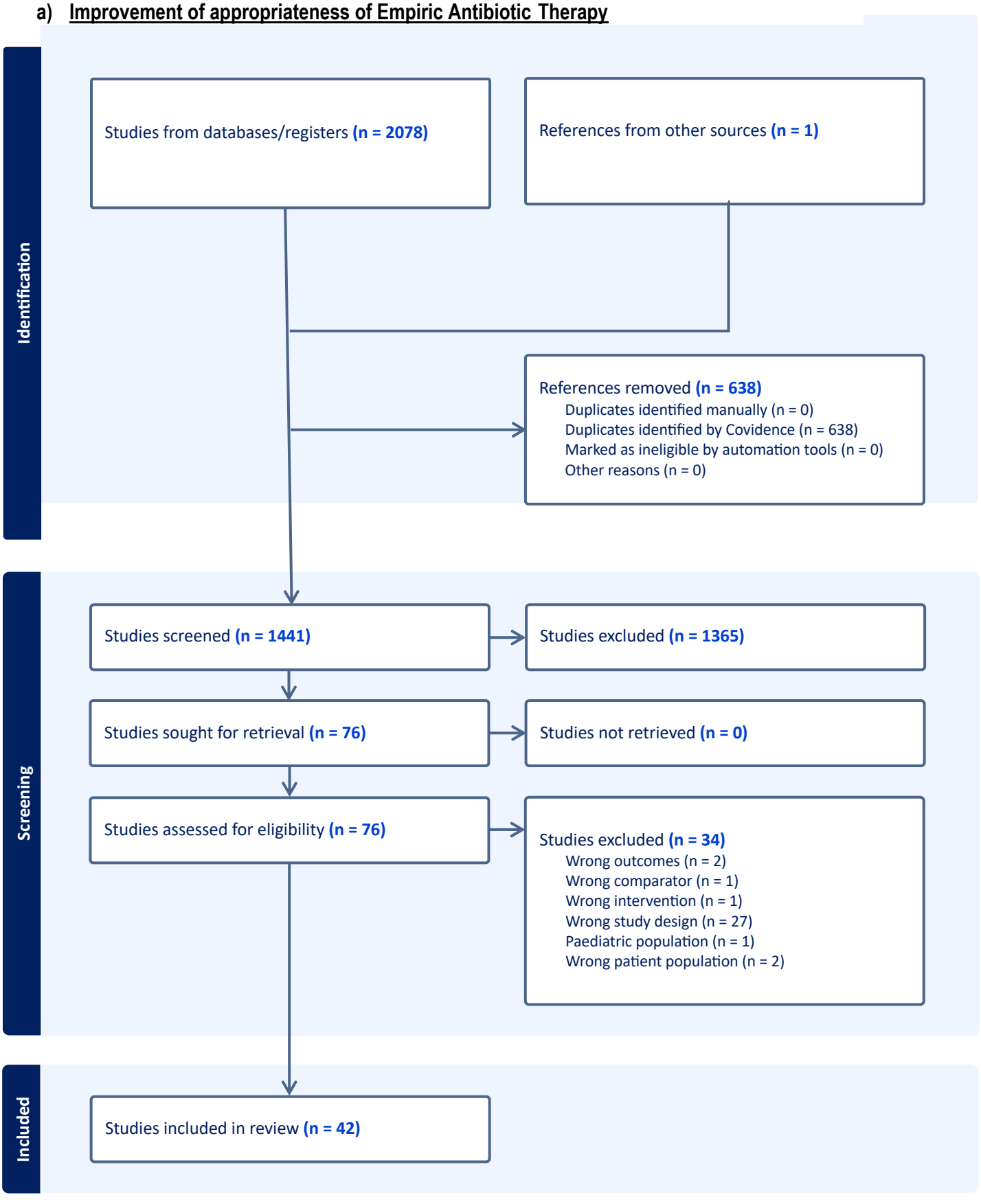
1. 'cystitis'/exp OR cystitis
2. 'pyelonephritis'/exp OR pyelonephritis
3. 'urinary tract infection'/exp OR 'urinary tract infection'
4. 'urinary tract infections'/exp OR 'urinary tract infections'
5. 'urinary tract infection'/exp
6. 'cystitis'/exp
7. 'pyelonephritis'/exp
8. ('cystitis'/exp OR cystitis) OR ('pyelonephritis'/exp OR pyelonephritis) OR ('urinary tract infection'/exp OR 'urinary tract infection') OR ('urinary tract infections'/exp OR 'urinary tract infections') OR 'urinary tract infection'/exp OR 'cystitis'/exp OR 'pyelonephritis'/exp
9. 'prognosis'/exp
10. prognos*:ab,ti
11. 'risk factor'/exp
12. predict*
13. 'risk'/exp OR risk
14. 'prognosis'/exp OR prognos*:ab,ti OR 'risk factor'/exp OR predict* OR ('risk'/exp OR risk)
15. 'antibiotic resistance'/exp OR 'antibiotic resistance'
16. 'antimicrobial stewardship'/exp OR 'antimicrobial stewardship'
17. 'bacterial resistance'/exp OR 'bacterial resistance'
18. 'antimicrobial resistance'/exp OR 'antimicrobial resistance'
19. 'antibiotic resistance'/exp
20. 'bacterial drug resistance'/exp OR 'bacterial drug resistance'
21. ('antibiotic resistance'/exp OR 'antibiotic resistance') OR ('antimicrobial stewardship'/exp OR 'antimicrobial stewardship') OR ('bacterial resistance'/exp OR 'bacterial resistance') OR ('antimicrobial resistance'/exp OR 'antimicrobial resistance') OR 'antibiotic resistance'/exp OR ('bacterial drug resistance'/exp OR 'bacterial drug resistance')
22. 'conference abstract':it
23. editorial:it
24. letter:it
25. news:it
26. newspaper:it
27. 'conference paper':it
28. 'conference review':it
29. 'conference abstract':it OR editorial:it OR letter:it OR news:it OR newspaper:it OR 'conference paper':it OR 'conference review':it
30. (('cystitis'/exp OR cystitis) OR ('pyelonephritis'/exp OR pyelonephritis) OR ('urinary tract infection'/exp OR 'urinary tract infection') OR ('urinary tract infections'/exp OR 'urinary tract infections') OR 'urinary tract infection'/exp OR 'cystitis'/exp OR 'pyelonephritis'/exp) AND ('prognosis'/exp OR prognos*:ab,ti OR 'risk factor'/exp OR predict* OR ('risk'/exp OR risk)) AND (('antibiotic resistance'/exp OR 'antibiotic resistance') OR ('antimicrobial stewardship'/exp OR 'antimicrobial stewardship') OR ('bacterial resistance'/exp OR 'bacterial resistance') OR ('antimicrobial resistance'/exp OR 'antimicrobial resistance') OR 'antibiotic resistance'/exp OR ('bacterial drug resistance'/exp OR 'bacterial drug resistance'))
31. ((('cystitis'/exp OR cystitis) OR ('pyelonephritis'/exp OR pyelonephritis) OR ('urinary tract infection'/exp OR 'urinary tract infection') OR ('urinary tract infections'/exp OR 'urinary tract infections') OR 'urinary tract infection'/exp OR 'cystitis'/exp OR 'pyelonephritis'/exp) AND ('prognosis'/exp OR prognos*:ab,ti OR 'risk factor'/exp OR predict* OR ('risk'/exp OR risk)) AND (('antibiotic resistance'/exp OR 'antibiotic resistance') OR ('antimicrobial stewardship'/exp OR 'antimicrobial stewardship') OR ('bacterial resistance'/exp OR 'bacterial resistance') OR ('antimicrobial resistance'/exp OR 'antimicrobial resistance') OR 'antibiotic resistance'/exp OR ('bacterial drug resistance'/exp OR 'bacterial drug resistance'))) NOT ('conference abstract':it OR editorial:it OR letter:it OR news:it OR newspaper:it OR 'conference paper':it OR 'conference review':it)
32. #31 AND [2000-2020]/py

Cochrane Library

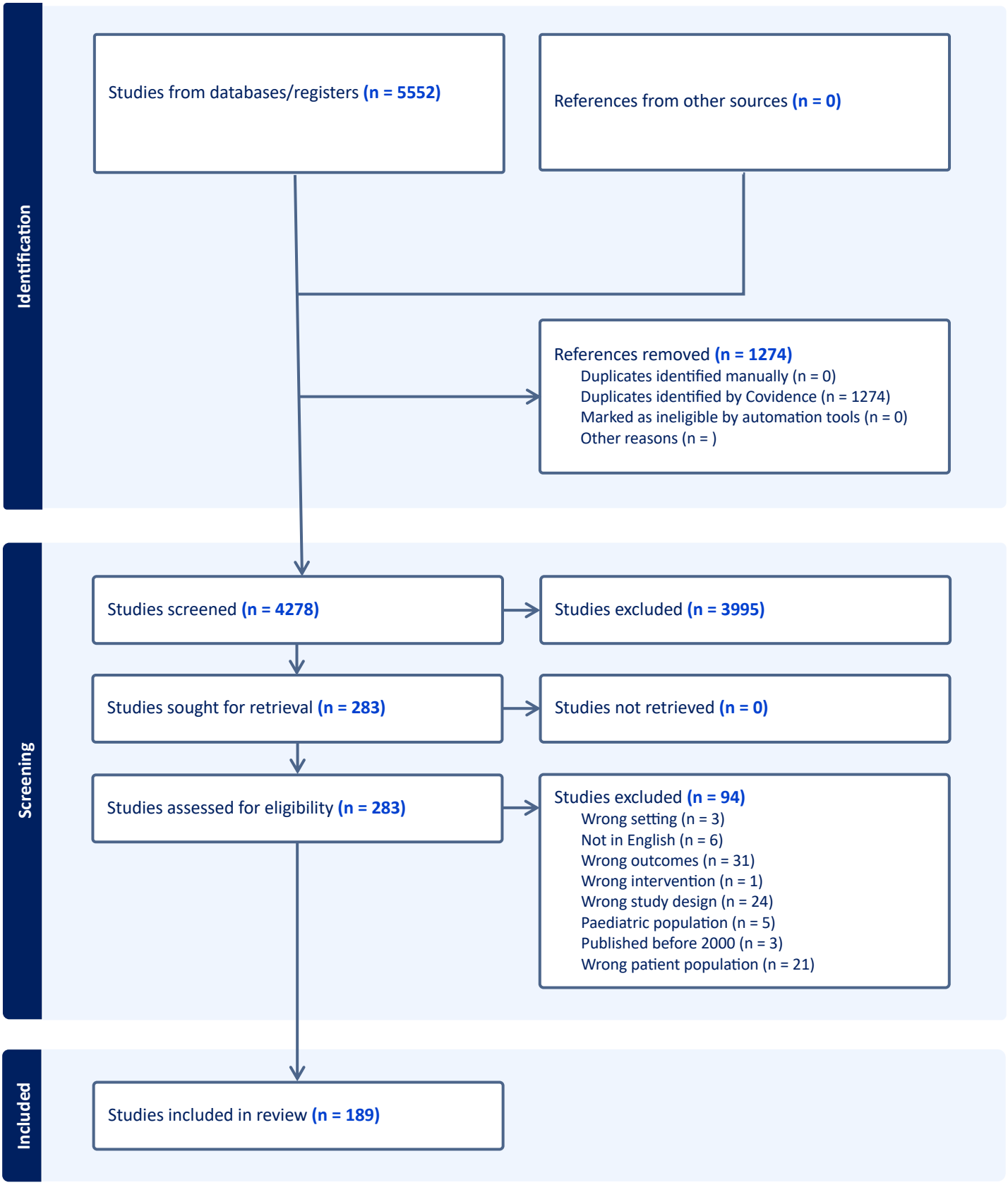
1. "urinary tract infection" OR cystitis OR pyelonephritis
2. MeSH descriptor: [Cystitis] explode all trees
3. MeSH descriptor: [Pyelonephritis] explode all trees
4. MeSH descriptor: [Urinary Tract Infections] explode all trees
5. #1 OR #2 OR #3 OR #4
6. MeSH descriptor: [Prognosis] explode all trees
7. MeSH descriptor: [Risk Factors] explode all trees
8. prognos* OR risk OR predict*
9. #6 OR #7 OR #8
10. MeSH descriptor: [Drug Resistance, Bacterial] explode all trees
11. "antibiotic resistance" OR "antibiotic resistant" OR "antimicrobial stewardship" OR "bacterial resistance" OR "bacterial resistant" OR "antimicrobial resistance" OR "antimicrobial resistant"
12. #10 OR #11
13. #5 AND #9 AND #12

Supplementary Figures B2: Prisma Flow Diagram of the study identification and selection (last updated September 1st, 2023)

a) **Improvement of appropriateness of Empiric Antibiotic Therapy**



b) **Risk factors for resistant uropathogens**



Step 2A: Value of prior urine cultures

Prior urine cultures' impact on appropriateness of antibiotic therapy

Supplementary Table B2A.1: Characteristics of the included studies (n=2, 2000-2023)

Study *(Lead author, Year of publication, Countries)*	**Population** *(Type UTI, Year of enrollment, n included, F (%), Age)*	**Study design** *(outcome of interest)*	**Organisms and Prevalence of resistance (***% and per classes, if provided)*	**Prior urine culture** *(% and definitions if provided)*	**Time frame of prior urine culture**	**Concordance between EAT and previous urine culture** (definition and stratification, if any)
Almomani 2020 **Jordan** **One center**	UTI, hospitalised adult and pediatric patients with prior ESBL-UTI episodes 2014-2019 N=483 patients, 693 patient episodes F:57% Age: 50y	Retrospective study Concordance between EAT used and previous urine culture	*E.coli* (82%) and *K. pneumoniae* (18%) First urine culture had to be an ESBL-producing organisms	When there were numerous previous cultures, the culture with a ESBL profile was used to determine the classification of concordant treatment	Between 14 days and 12 months Median interval between paired isolates was 3 months	Concordance: if adequate according to guidelines and previous microbiological data Stratified by time frames
Lisenmeyer 2015 **USA** **Multicenter**	MDR UTI, inpatient and outpatient settings (3 VA facilities) 2010-2013 N=101 patients, 126 patient episodes F=10% Age: 73y	Retrospective study Concordance between EAT used and previous urine culture	*E.coli* (60%) and *Klebsiella spp* (39%) Current episode with a multidrug-resistant Gram-negative organisms (3 or more classes of antibiotics) Specific resistance: 3rd gen cephalosporins: 99%, FQ: 84%, TMP/SMX 63%, nitrofurantoin 38%, carbapenems 2%	When there were numerous previous cultures, the culture with a profile with the most resistance was used to determine the classification of concordant treatment Available for 95 patient episodes	Within 6 months, but id not available then within 2 years Available within 6 months: 73% and within 6 months and 2 years: 27%	Concordance: activity against all previously isolated Gram-negative uropathogens Stratified by: 1) Antibiotic classes: GU-directed agents (nitrofurantoin, TMP/SMX and fosfomycin), broad-spectrum agents (carbapenems and anti-pseudomonal beta-lactams), and other agents (fluoroquinolones, aminoglycosides, and all other non-pseudomonal beta-lactams) 2) Time frames: within 6 months or within 2 years

UTI: Urinary Tract Infection; ESBL: Extended Spectrum Beta-Lactamase; MDR: Multidrug resistant; N: number; F: female, y: years; NR: not reported
EAT: Empiric Antimicrobial Therapy; FQ: Fluoroquinolone; TMP/SMX: trimethoprim/sulfamethoxazole; GU: genitourinary

Supplementary Table B2A.2: Assessment of the Risk of bias of included studies (QUIPS tool)

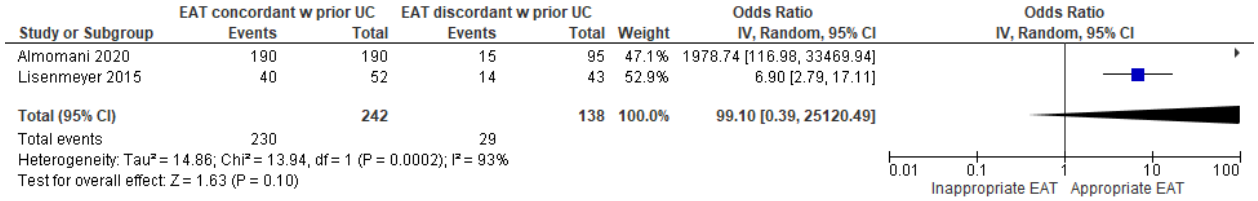
Studies	Overall Risk of bias	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Almomani 2020	**High**	Only in patients with prior ESBL-UTI episodes / Paired culture requirement might have overrepresented the recurrent UTI population	Only 42% (285/683) of paired urine cultures were fully analyzed due mainly to the knowledge of the results of urine culture on admission (definitive rather than empiric therapy)	Based on prior more resistant urine culture results all participants	Appropriateness of EAT for current UTI episode based on index urine culture in all participants	Adjusted for time frames between urine cultures but not adjusted for other individual factors (e.g. intervening receipt of antibiotics) potentially influencing appropriateness of EAT	Multivariate analysis
Lisenmeyer 2015	**High**	Only in patients with current MDR UTI episodes / Paired culture requirement might have overrepresented the recurrent UTI population	75% (95/126) of UTI episodes had prior data and were fully analyzed	Based on prior (more resistant) urine culture results in all participants	Appropriateness of EAT for current UTI episode based on index urine culture in all participants	Stratified for time frames between urine cultures, but not adjusted for other individual factors (e.g. intervening negative culture or intervening receipt of antibiotics) or local practices potentially influencing appropriateness of EAT	Stratified analysis

QUIPS: Quality in Prognostic Studies
ESBL: Extended Spectrum Beta-Lactamase; MDR: Multidrug resistant; UTI: urinary tract infection; EAT: empiric antimicrobial therapy

Risk of bias judgement

Low	
Moderate	
High	

Supplementary Figures B2A.1: Forest plot for the impact of prior urine cultures on appropriateness of empiric antibiotic therapy



EAT: empiric antibiotic therapy; "w prior UC": with prior urine culture.
*Due to the perfect appropriateness of EAT when based on the results of prior urine culture in the Almomani 2020 study, it is impossible to provide a precise pooled estimate for the odds ratio.

Supplementary Table B2A.3: Certainty of evidence for the impact of prior urine cultures on appropriateness of empiric antibiotic therapy (using the GRADE approach)

Risk factors	Risk of bias	Consistency	Directness	Precision	Publication bias	Overall
Prior urine culture	Very serious*	Not serious**	Not serious	Not serious	None suspected	Low

*Rated down for risk of bias due to the high risk of bias (study design and residual confounding)
**Despite a I-square of 93%, this inconsistency is not considered significant for the decision-making process.

Supporting evidence

Predictive values of prior urine culture for current susceptibility or resistance in patients with paired urine cultures

Methods

The aim of the studies included in this section was to identify diagnostic test accuracy of studies that reported on the **value of susceptibilities in a prior urine culture to predict antibiotic susceptibilities in the current urine culture** of patients suspected of having a UTI. We included studies that been published between 2000 and present (2023) based on adult patients suspected of UTI from any geographic location. Studies could be based on laboratory data without requiring clinical confirmation of UTI, as long as they measured the correlation of susceptibility and resistance among common Gram-negative uropathogens in urine cultures from the same patient (all patients had paired urine cultures).

Supplementary Table B2A. 4: Characteristics of the included studies (n=4, 2000-2023)

Study *(Lead author, Year of publication, Countries)*	**Population** *(Type UTI, Year of enrollment, n included, F (%), Age)*	**Study design** *(outcome of interest)*	**Organisms and Prevalence of resistance (***% and per classes, if provided)*	**Time frame of prior urine culture**	**Adjustment for other variables**
MacFadden 2014 USA and Canada (multicenter)	Outpatients and inpatients with suspicion of UTI 2010-2012 N: 4,351 patients with 22,019 paired positive cultures (of which 9,590 recovered the same organism and were further tested for predictive value of susceptibility profile) F: 80% Age: 72y	Retrospective study Predictive value of prior organism identification and susceptibility profile to index urine cultures	Mainly *E. coli*, *Klebsiella spp.* and *Pseudomonas spp.* The resistance rates: -cipro-R bacteria: 40%	From 4 weeks to more than 32 weeks	Variables considered in the multivariate analysis: patient demographics (age and sex), hospital variables (city/ward/ service, outpatient/inpatient status), culture variables (date and time of clinical specimen collection, identities and susceptibilities of isolates, a negative urine culture collected between the paired positive cultures), and treatment variables (antibiotic use between collection of paired positive cultures). Stratification based on city, receipt of intervening antimicrobial therapy, and organism type
Dickstein 2016 Israel (one center)	Inpatients with suspicion of UTI 2011-2015 N: 4,409 patients with 19,546 paired positive cultures F: 53% Age: 70y	Retrospective study Predictive value of prior resistance phenotypes to index urine cultures	Ciprofloxacin-R Gram-negative bacteria, ESBL-producing Enterobacteriaceae, carbapenem-resistant *Enterobacteriaceae* (CRE), or carbapenem-resistant non-fermenters (CRNF; including *Pseudomonas* and *Acinetobacter spp*). The resistance rates: -ciprofloxacin-R: 49.9% -ESBL-producing Enterobacteriaceae: 26.5% -CRE:1.7% -CRNF: 2.8%	From 14 days to 60 months	Risk factors considered in the multivariate analysis: age, gender, time between cultures, intervening cultures without resistance, service (ER, surgery, ICU or medicine) Stratification per resistance phenotype
Vellinga 2010 Ireland	Outpatients with recurrent bacteriuria 2004-2008 N: 3,413 patients with paired *E..coli*-positive urine samples F:91% Age: 52y	Retrospective study Predictive value of prior susceptibility / resistance profile to index urine cultures	*E. coli*: 100% The resistance rates: -amoxiclav: 23.9% -ampicillin: 60.7% -ciprofloxacin: 5.7% -nitrofurantoin: 2.6% -trimethoprim: 26.4%	From 14 days to 12 months	Stratification per antibiotics
Valentine-King 2023 USA	Outpatients with recurrent uUTI 2016-2018 N:165 patients with Gram-negative organisms F: 97% Age: 63y	Retrospective study Predictive value of prior susceptibility / resistance profile to index urine cultures	Gram-negative organisms The resistance rates in *E. coli*: -ampicillin: 57% -ciprofloxacin: 28% -nitrofurantoin: 5% -trimethoprim-sulfamethoxazole: 38%	From 3 days to 24 months	Stratification per antibiotics

UTI: urinary tract infection; uUTI: uncomplicated UTI; N: number; F: female, y: years; R: resistant, including non-susceptible;; ESBL: extended spectrum beta-lactamase; ER: emergency room; ICU: intensice care unit.

Supplementary Table B2A.5: Estimating predictive values of prior urine cultures for current uropathogen susceptibility (NPV) or resistance (PPV)

Antibiotics	Negative predictive value (NPV)	Positive predictive value (PPV)	Interval between cultures	Prevalence of resistance	References
General	83% (81 to 85%)	NR	4-8 weeks		McFadden 2014
	75% (73 to 77%)	NR	More 32 weeks		McFadden 2014
Fluoroquinolones	98.3% (97.8 to 98.7%)	83.8% (71.7 to 90.7)	Within 3 months	Cipro-R 6%	Vellinga 2010
	94% (85 to 98%)	84% (60 to 97%)	Median 3.5 months	Cipro-R 28%	Valentine-King 2023
	47% (46 to 48%)	68% (66 to 69%)	Up to 6 months (median 34)	Cipro-R 48%	Dickstein 2016
	96.8% (96.0 to 97.5%)	43.4% (30.1 to 56.9%)	Between 9-12 months	Cipro-R 6%	Vellinga 2010
	85% (83 to 87%)	NR	More 32 weeks	Cipro-R 40%	McFadden 2014
Third generation cephalosporins	72% (71 to 72%)	56% (54 to 58%)	Up to 6 months	ESBL:31%	Dickstein 2016
TMP/SMX	91.3% (89.9 to 92.5%)	78.3% (73.1 to 82.5%)	Within 3 months	TMP/SMX-R 26%	Vellinga 2010
	81% (71 to 87%)	57% (34 to 78%)	Median 3.5 months	TMP/SMX-R 38%	Valentine-King 2023
	86.3% (83.6 to 88.6%)	59.2% (51.9 to 66.0%)	Between 9-12 months	TMP/SMX-R 26%	Vellinga 2010
Carbapenems	98% (98 to 98%)	48% (40 to 56%)	Up to 6 months	CRE: 2%	Dickstein 2016

NPV: negative predictive value, or the probability of a prior susceptible organism in urine culture to accurately predict future susceptibility; PPV: positive predictive value, or the probability of a prior resistant organism in urine culture to accurately predict future resistance; NR: not reported; R: resistance; Cipro: ciprofloxacin; ESBL: extended spectrum beta lactamase; TMP/SMX: trimethoprim/sulfamethoxazole; CRE: carbapenem-resistant Enterobacterales

Limitations

Studies reporting on the predictive values of prior urine culture likely selected for patients presenting with recurrent UTI, as a consequence of the paired culture requirement. Therefore, the results may not be completely generalizable to patients presenting with complicated UTI.

Prior uropathogen resistance to a specific antibiotic as a risk factor for current resistance

Methods

The aim of the studies included in this section was to identify studies that reported on the predictive **value of uropathogen resistance to a specific antibiotic in a prior urine culture to predict resistance in the urine culture of the current UTI episode**. We included studies that had been published between 2000 and present (2023) and reported on North American populations (United States, Canada, and Mexico), as risk factors for antibiotic resistance will vary depending on the local epidemiology. Included studies had to report on adults with UTI, meaning that studies that were based on laboratory data only (i.e. without a confirmed clinical diagnosis of UTI) were excluded. We included cohort and case-control studies that reported on risk factors for specific resistance among common Gram-negative uropathogens. At least a portion of the patients enrolled in a specific study needed to have a prior urine culture for that study to be included in our review. Finally, studies meeting these criteria were included only if they reported adjusted relative risks using a multivariate analysis.

Supplementary Table B2A.6: Characteristics of the included studies (n=3, 2000-2023)

Study *(Lead author, Year of publication, Countries)*	**Population** *(Type UTI, Year of enrollment, n included, F (%), Age)*	**Study design** *(outcome of interest)*	**Organisms and Prevalence of resistance (***% and per classes, if provided)*	**Time frame of prior urine culture**	**Adjustment for other variables**
De Marsh 2020 USA (multicenter)	Inpatient and Outpatient with community-onset UTI due to Enterobacteriaceae 2015-2016 N=351 patients F: 72% Age: 64y	Retrospective case-control study Predict resistance to TMP-SMX resistance	Enterobacteriaceae Prevalence of resistance to trimethoprim/sulfamethoxazole: 20.2%	Within 12 months	Variables considered for the multivariate analysis: age, sex, ethnicity, diabetes mellitus, cancer, immunocompromised host, recent hospitalisation within 3 months, residence in a skilled nursing facility, ambulatory gastrointestinal or genitourinary procedure within 1-month, prior UTI or urinary colonisation with TMP/SXT-R bacteria within 12 months, and prior antimicrobial use within 12 months.
Cooley 2020 USA (one center)	Outpatient with afebrile cystitis <u>Training population:</u> 2012-2016 cohort (algorithm N=2,891 patients, of which 705 had a prior urine culture (31.4%) <u>Testing population</u> 2017-2018 N= 646 patients, of which 294 had prior urine culture (46%) F: 60% Age: 60y	Retrospective cross-sectional study Test a pragmatic algorithm to predict resistance	Uropathogens (mainly *E. coli* 61%, *Enterococcus* spp 12% and *Klebsiella pneumoniae* 10%) Prevalence of resistance were 19.5% for fluoroquinolones, 25.6% for trimethoprim/sulfamethoxazole and 6.9% for third generation cephalosporins	Within 6 years	Covariates included patient demographics (age, race, and ZIP code), any antimicrobial prescriptions within the past 2 years, past urine culture results and department to which patient presented. Stratified by antibiotic class
Cohen 2020 USA	Outpatient with uUTI <u>Training population:</u> 2011-2017 N=9,455 patients, of which 1,978 had prior urine culture <u>Testing population:</u> 2018 N= 646 patients, of which 258 had prior urine culture F: 100% Age: 49y	Retrospective data Test a pragmatic algorithm to predict resistance	Uropathogens (mainly *E. coli* 74%, Group B *Streptococcus* (6%), *Klebsiella pneumoniae* 6%), *Enterococcus spp* 3%) Prevalence of resistance varied from 10.3% for fluoroquinolones,12.1% to nitrofurantoin, and 19.4% for trimethoprim/sulfamethoxazole	Within 6 years	Covariates included patient demographics (age, race, and ZIP code), any antimicrobial prescriptions within the past 2 years, past urine culture results and department to which patient presented. Stratified by antibiotic class
Please note that the Cooley 2020 study and the Cohen 2020 study were performed on the same database, for almost the same time period. However, the patient populations should have differed, since one set had complicating factors as per ICD codes, and the other set did not have these complicating factors.					
UTI: urinary tract infection; uUTI: uncomplicated UTI; N: number; F: female, y: years; TMP/SMX: trimethoprim/sulfamethoxazole; ZIP: Zone Improvement Plan; ICD: International Classification of Diseases					

Step 2B: Risk factors for resistance to a specific antibiotic class

Methods

Initially, all risk factors reported as independently associated with resistance to a specific antibiotic were considered for further analysis such as: demographics (age, gender, and ethnicity), comorbidities (such as diabetes, chronic kidney disease, malignancies, immunosuppression), prior genitourinary history (urinary catheterization, obstructive uropathy, recent GU procedure, prior UTI, recurrent UTI), prior antibiotic use (stratified by class and time frame), recent healthcare exposure (residence in a nursing home or long term care facility, and recent hospitalisation), and recent travel (stratified by continent). To ensure that we had captured factors that might predict having an organism resistant to a specific antibiotic, we looked also at factors which were associated with receiving IEAT. These included hospitalization within six months, having an indwelling urinary catheter, and having received antibiotics in the prior month (Rodriguez-Gomez 2019, Korkmaz 2020).

Risk factors of fluoroquinolones resistance

Supplementary Table B2B.1: Characteristics of the studies included for risk factors of fluoroquinolones resistance (n=7, 2000-2023)

Study *(Lead author, Year of publication, Countries)*	**Population** *(Type UTI, Year of enrollment, n included, F (%), Age)*	**Study design** *(outcome of interest)*	**Organisms and Prevalence of FQ-resistance**	**Time frame of risk factors**	**Other independent predictors of resistance**
Cohen 2006 Pennsylvania (USA)	LTCF-acquired mixed UTI (confirmed with McGeer criteria) 2000-2004 N=165 F: 0% (exclusion criteria) Age: 75y	Retrospective matched case control 1:4 (controls were randomly selected in patients with a length of stay of at least 1 week and resident in the LTCF on the date of cases' positive cultures)	Only E coli included FQ-R E. coli: 45%	Antibiotic use in the prior 6 months (for FQ, number of days, number of courses and time between first FQ exposure and FQ-R *E. coli*)	-Urinary catheterization
Johnson 2008 Denver, Colorado (USA)	Mixed UTI (uUTI and CA-UTI), outpatient clinics (including emergency and urgent care clinics) 2005 N=123 F: 83% Age: 56y	Retrospective matched case-control 1:2 (controls were matched by sex, clinic site and age)	Only *E coli* included Levo-R E. coli: 9.4%	Previous levofloxacin use in the last 12 months	-Previous weeks of hospitalization within last 12 months
Khawcharoenporn 2012 Chicago, Illinois (USA)	Mixed UTI in ED 2008-2009 N=337 F:83% Age: 38y	Retrospective study	*E. coli* 71%, *Klebsiella spp*. (9%) Levo-R: 17%	Prior quinolone use within 3 months (stratified for less than 1 week and 1-4 weeks)	-Long-term medical conditions -Healthcare associated infection
Killgore 2004 San Francisco, California (USA)	Mixed UTI in ED or outpatient clinics 2001 N=120 F: 85% Age: 61y in cases and 51 in controls	Retrospective case-control 1:2 study (controls were selected randomly during the same time period)	Only *E.coli* Cipro-R -outpatient: 10% -inpatient : 21%	Previous use of any quinolone during 4 weeks prior to presentation with UTI symptoms	-Recurrent UTI
Rattanaumpawan 2010 Pennsylvania, USA	Healthcare-acquired UTI (defined as per CDC) 2003-2005 N=514 F: 67% Age: 69y in cases and 68y in controls	Retrospective case-control study (controls were matched by the month of isolation and the species of the infecting organism)	Gram-negative bacilli (Among the cases: *E.coli* 51%, *P. aeruginosa* 22%) FQ-R: 15.6%	Recent inpatient antibiotic exposure to fluoroquinolones in the preceding 30 days	-Male sex -African-American ethnicity -Chronic respiratory disease -Residence in a long-term care facility -Previous hospitalisation within 2 weeks -Hospitalisation under a medicine service -Recent inpatient antibiotic exposure in prior 30 days (cotrimoxazole, metronidazole)
Rich 2022 North-Central Florida (USA)	Mixed UTI inpatient or outpatient 2011-2019 N=9,990 of which 1,977 patients were used in the model for FQ	Retrospective (chart review)	*E. coli* 59%, *Klebsiella pneumoniae* 15%	Prior ciprofloxacin use (unclear time frame)	-Age -Sex -Diabetes -Renal disease -Hemiplegia or paraplegia -History of UTI

	F: 76% Age: 61y				-Non-fluoroquinolone antibiotic
Shah 2017 Palmetto, South Carolina (USA)	cUTI April to July 2015 N=238 F: 68% Age: 66y	Prospective identification of cases and controls by microbiology alerts	Gram-negative bacilli (*E. coli* 58%, *Klebsiella pneumoniae* 16%) Overall FQ-R: 23%	Fluoroquinolone exposure up to 12 months (stratified for up to 3 months and within 3-12 months)	-Male sex -Diabetes mellitus -Residence at a skilled nursing facility -Outpatient GI/GU procedure within prior month
UTI: Urinary Tract Infection; cUTI: complicated UTI; uUTI: uncomplicated UTI; CA-UTI: catherter-associated UTI; LTCF: long-term care facility; ED; emergency department; N: number; F: female, y: years; FQ: fluoroquinolone; Levo: levofloxacin; cipro: ciprofloxacin; R: resistant; GI/GU: gastrointestinal/ genitourinary.					

Supplementary Table B2B.2: Assessment of the Risk of bias of included studies (n=7) (QUIPS tool)

	Overall Risk of bias	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Cohen 2006	High	LTCF male patients	Missing data not reported	More information assessed on prior FQ use in the FQ-R group	Unclear if McGeer criteria were used for controls as well	Probable residual confounding	Multivariate conditional logistic regression but small sample size
Johnson 2008	High	Outpatients	Missing data not reported	Chart review	Low	Probable residual confounding	Multivariate conditional logistic regression but small sample size
Khawcharoenporn 2012	Moderate	Patients discharged from ED	Missing data not reported	Chart review but with data-gathering form	Low	Possible residual confounding	Multivariate logistic regression
Killgore 2004	High	ED or outpatients	Missing data not reported	Chart review	Low	Probable residual confounding	Multivariate logistic regression but small sample size
Rattanaumpawan 2010	High	Patients with HA UTI	Missing data not reported	Chart review	Low	Possible residual confounding	Multivariate logistic regression (conditional should have been used with matched case-control study)
Rich 2022	High	UTI	Missing data not reported	Chart review and time frame not reported	Low	Possible residual confounding	Multivariate logistic regression
Shah 2017	Moderate	cUTI	Missing data not reported	Chart review	Low	Possible residual confounding	Multivariate logistic regression

QUIPS: Quality in Prognostic Studies
LTFC: long-term care facility; ED: emergency department; HA: heathcare-associated; UTI: urinary tract infection; cUTI: complicated UTI; FQ: fluoroquinolone; R: resistant

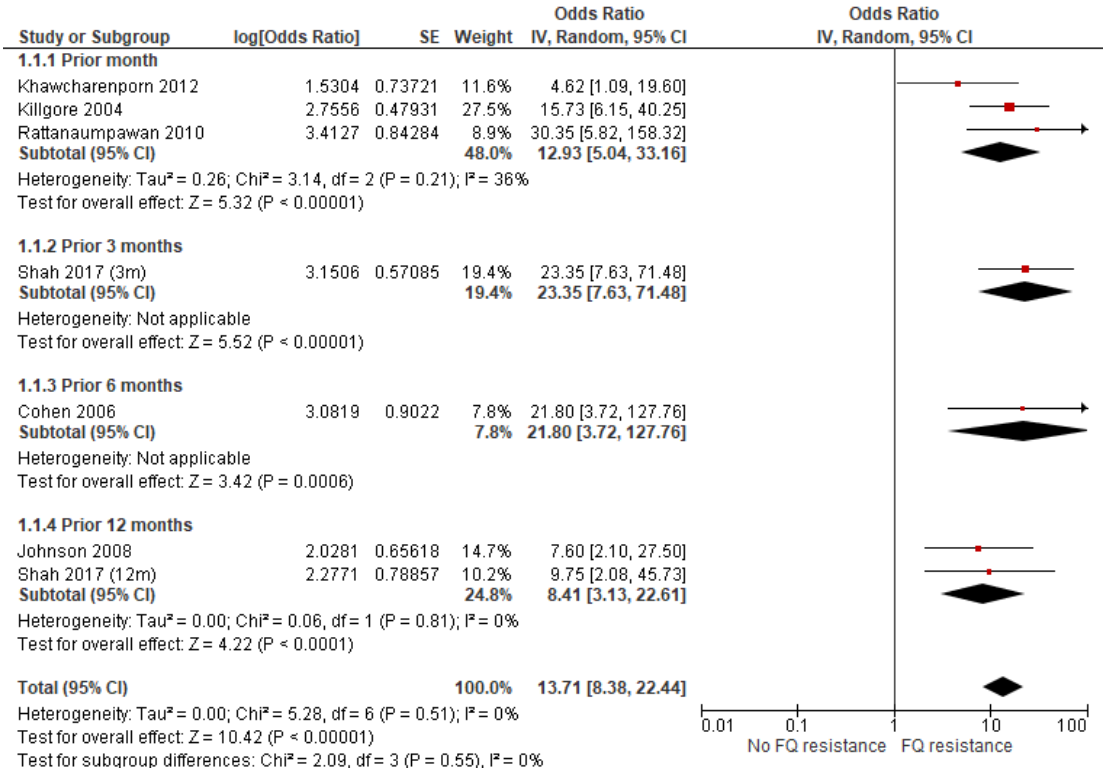
Risk of bias judgement

Low	
Moderate	
High	

Limitations

All of these studies were retrospective and observational. The populations were heterogeneous, as were the risk factors included in analyses. Statistical modeling approaches varied across studies. Small sample size in some studies also contributed to imprecision in risk factor estimates.

Supplementary Figure B2B.1: Forest plot for the impact of time interval between prior fluoroquinolone exposure on the fluoroquinolone resistance in UTI



Supplementary Table B2B.3: Certainty of evidence for the impact of prior fluoroquinolone exposure on fluoroquinolone resistance UTI (using the GRADE approach)

Risk factors	Risk of bias	Consistency	Directness	Precision	Publication bias	Overall
Prior use of fluoroquinolones	Very serious*	Not serious	Not serious	Not serious	Publication bias suspected	Very low

*Rated down for risk of bias due to the high risk of bias (study design and residual confounding)

Step 4: Antibiogram (for septic patients due to cUTI)

Modeling to establish antibiogram thresholds

Model inputs, assumptions and judgments:

1) Baseline mortality in patients presenting with cUTI and receiving appropriate empiric antibiotic therapy approximates:
   - -20% in cUTI patients with septic shock admitted to ICU
   - -10% in cUTI patients with sepsis without shock
   - -5% in cUTI patients without sepsis
2) Based on our conservative estimate of the impact of IEAT on mortality:
   - -adjusted OR = 1.56, 95% CI (0.99 to 2.46) / very low certainty of evidence
3) Panel judged the aim of using an antibiogram was to avoid one excess death per 100 patients due to inappropriate empiric antibiotic therapy

Septic shock in ICU (baseline mortality 20%)

Our modeling suggests that to avoid one excess death due to inappropriate empiric antibiotic therapy per 100 patients with a baseline risk of mortality of 20%, antibiotics should only be selected if the thresholds for antibiotic susceptibility from the antibiogram is more than 90%.

Supplementary Table B4.1: Modeling in patients with cUTI and associated with septic shock in ICU

	5% Resistance		10% Resistance		15% Resistance		20% Resistance		25% Resistance	
Baseline mortality: 20%	**IEAT (NS)**	**AEAT (S)**	**IEAT (NS)**	**AEAT (S)**	**IEAT (NS)**	**IEAT (NS)**	**IEAT (NS)**	**AEAT (S)**	**IEAT (NS)**	**AEAT (S)**
	0.05* 20.0* 1.56	0.95* 20.0	0.1* 20.0* 1.56	0.9* 20.0	0.15* 20.0* 1.56	0.85* 20.0	0.20* 20.0* 1.56	0.80* 20.0	0.25* 20.0* 1.56	0.75* 20.0
	1.6	19.0	3.1	18.0	4.7	17.0	6.2	16.0	7.8	15.0
	20.6%		**21.1%**		**21.7%**		**22.2%**		**22.8%**	
20 deaths per 100 patients			**+ 1 death per 100 cUTI as compared to baseline**							
200 deaths per 1000 patients	**+6 deaths per 1000 cUTI as compared to baseline**		**+11 deaths per 1000 cUTI as compared to baseline**		**+17 deaths per 1000 cUTI as compared to baseline**		**+22 deaths per 1000 cUTI as compared to baseline**		**+28 deaths per 1000 cUTI as compared to baseline**	

Sepsis without shock (baseline mortality 10%)

Our modeling suggests that to avoid one excess death due to inappropriate empiric antibiotic therapy per 100 patients with a baseline risk of mortality of 10% (sepsis without shock), antibiotics should only be selected if the thresholds for antibiotic susceptibility from the antibiogram is more than 80%.

Supplementary Table B4.2: Modeling in patients with cUTI and associated sepsis without shock

	5% Resistance		10% Resistance		15% Resistance		20% Resistance		25% Resistance	
Baseline mortality: 10%	**IEAT (NS)**	**AEAT (S)**	**IEAT (NS)**	**AEAT (S)**	**IEAT (NS)**	**IEAT (NS)**	**IEAT (NS)**	**AEAT (S)**	**IEAT (NS)**	**AEAT (S)**
	0.05* 10.0* 1.56	0.95* 10.0	0.1* 10.0* 1.56	0.9* 10.0	0.15* 10.0* 1.56	0.85* 10.0	0.20* 10.0* 1.56	0.80* 10.0	0.25* 10.0* 1.56	0.75* 10.0
	0.8	9.5	1.6	9.0	2.34	8.5	3.1	8.0	3.9	7.5
	10.3%		**10.6%**		**10.8%**		**11.1%**		**11.4%**	

10 deaths per 100 patients				**+ 1 death per 100 cUTI as compared to baseline**	
100 deaths per 1000 patients	**+3 deaths per 1000 cUTI as compared to baseline**	**+6 deaths per 1000 cUTI as compared to baseline**	**+8 deaths per 1000 cUTI as compared to baseline**	**+11 deaths per 1000 cUTI as compared to baseline**	**+14 deaths per 1000 cUTI as compared to baseline**

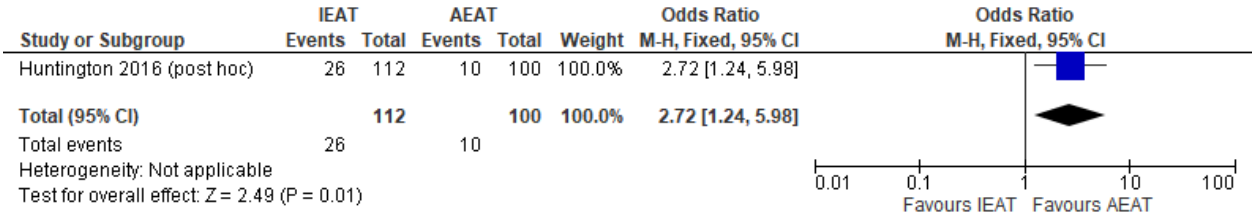
Without sepsis (5%)

Our modeling suggests that to avoid one excess death due to inappropriate empiric antibiotic therapy per 100 patients with a baseline risk of mortality of 5% (without sepsis such as patients discharged from emergency department or clinic, or admitted to non-ICU ward), antibiotics should only be selected if the thresholds for antibiotic susceptibility from the antibiogram is more than 60%.

Supplementary Table B4.3: Modeling in patients with cUTI without associated sepsis

	10% Resistance		**20% Resistance**		**30% Resistance**		**35% Resistance**		**40% Resistance**	
Baseline mortality: 5%	**IEAT (NS)**	**AEAT (S)**	**IEAT (NS)**	**IEAT (NS)**	**IEAT (NS)**	**AEAT (S)**	**IEAT (NS)**	**IEAT (NS)**	**IEAT (NS)**	**AEAT (S)**
	0.1* 5.0* 1.56	0.9* 5.0	0.20* 5.0* 1.56	0.80* 5.0	0.30* 5.0* 1.56	0.70* 5.0	0.35* 5.0* 1.56	0.65* 5.0	0.40* 5.0* 1.56	0.60* 5.0
	0.8	4.5	1.6	4.0	2.3	3.5	2.73	3.25	3.1	3.0
	5.3%		**5.6%**		**5.8%**		**6.0%**		**6.1%**	
5 deaths per 100 patients									**+ 1 death per 100 cUTI as compared to baseline**	
200 deaths per 1000 patients	**+3 deaths per 1000 cUTI as compared to baseline**		**+6 deaths per 1000 cUTI as compared to baseline**		**+8 deaths per 1000 cUTI as compared to baseline**		**+10 deaths per 1000 cUTI as compared to baseline**		**+11 deaths per 1000 cUTI as compared to baseline**	

Supplementary Figure B4.1: Forest plot for Clinical failure (Crude analysis from post-hoc analysis (Huntington 2016))



Definition of "Clinical Cure" was defined as complete resolution/significant improvement of the signs and symptoms of the index infection, with no additional antibiotics. Post-hoc analysis was performed in levofloxacin-resistant uropathogens. Antibiotics studied were ceftolozane/tazobactam vs levofloxacin. Of note, this is the only evidence free of confounding-by-indication since originating from randomised controlled trial, but still a post-hoc analysis.

Supplementary Table: GRADE Evidence to decision framework (general concepts used for the decision-making process)

POPULATION:	In patients presenting with complicated UTI
INTERVENTION:	Antibiotic A
COMPARISON:	Antibiotic B
MAIN OUTCOMES:	Clinical cure, recurrence of Infection, mortality, serious adverse events and non-serious adverse events
SETTING:	Inpatient and outpatient

Assessment

Problem
Is the problem a priority?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ **Yes**	Refer to Introduction for description of importance of this clinical question	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ **Varies**	Refer to the EP tables for each class of selected antibiotics for more information on clinical efficacy (i.e. clinical cure at TOC). As a general conclusion: when assuming susceptibility of uropathogen(s), all selected classes of antibiotics show comparable clinical efficacy.	The panel agrees that the main driver of clinical failure is inappropriate empirical antibiotic therapy due to resistance of the uropathogen(s). Consequently, a **stepwise approach** was developed to optimize the initial choice of antibiotics.

Undesirable effects
How substantial are the undesirable anticipated effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ **Varies**	Refer to the EP tables for each class of selected antibiotics for more information on adverse events. As a general conclusion: most antibiotics were considered comparable, except for older aminoglycosides.	The panel agrees to classify older aminoglycosides as an alternative therapy (rather than a preferred therapy) due to their unfavorable adverse events profile.

Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ **Varies**	Refer to the EP tables for each class of selected antibiotics for more information on the balance of effects.	The panel agrees that the main driver of the balance of effect was clinical failure (and thus the **stepwise approach**), except for antibiotics mentioned to have significant adverse events.
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ **Very low** to ○ **Moderate**	The certainty of evidence was moderate for all classes of selected antibiotics, except for 3rd and 4th generation cephalosporins, and older aminoglycosides, for which the certainty of evidence was very low.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ **Probably no important uncertainty or variability**		This guideline recommendation addresses which antibiotics to choose at that critical point at which the patient with cUTI presents for care and the causative organism has not yet been identified (empiric antibiotic choice). Empiric antibiotics typically are continued for up to 72 hours before being replaced with antibiotics tailored based on culture results and other emerging data. In that context, avoiding mortality by choosing initially appropriate antibiotic therapy is the most important outcome. When expected mortality is low, consultation with the patient representatives participating in this guidelines panel further supported that treatment (whatever the choice of empirical therapy) should mainly focus on achieving clinical cure. If clinical cure is expected to be similar between different treatments, additional considerations include antibiotic-associated adverse events, decreasing the risk of recurrence of infection, and avoiding readmission to hospital. Reducing the length of hospitalization and facilitating the ease of administration were considered important, but the choice of antibiotics by itself was not a driving factor in their decision-making process.
Costs and resources		
Resources required How large are the resource requirements (costs)?		
JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ **Varies**	It is not possible for the guidelines panel to offer nationally generalizable direct comparisons of cUTI antibiotic costs because (at least in the United States) these costs vary widely based on the drug wholesaler and their contracts with individual pharmacies and institutions. That said, at the time of development of these recommendations, the average wholesaler prices reported by the drug cost analysis tool Medi-Span (https://www.wolterskluwer.com/en/solutions/medi-	The panel agrees to classify newer antibiotics as alternative therapies (rather than a preferred therapies), especially if associated with higher resource requirements.

	span) suggests the antibiotics studied for cUTI can be categorized into three cost groups: low, medium, and high. Levofloxacin and ceftriaxone can be considered low-cost, with daily costs ranging from about $1 to about $50. Piperacillin-tazobactam and the carbapenems can be considered medium cost, with daily costs ranging from about $15 to about $150. Plazomicin, cefiderocol, and the novel cephalosporin and carbapenem beta-lactamase inhibitor combinations can be considered high-cost, with daily costs ranging from about $500 to $1500. Thus, the potential excess cost of a 7-day course of cUTI treatment with agents other than levofloxacin or ceftriaxone is on the scale of a few hundred to a thousand dollars for piperacillin-tazobactam or the carbapenems, or several thousand to ten thousand dollars for the novel agents. Additionally, we consider that all of these antibiotic agents are given IV except for levofloxacin and ertapenem (which have oral and IM formulations, respectively), and thus would at minimum incur additional costs in the hundreds to thousands-dollar range for administration of outpatient parenteral antibiotic therapy (OPAT). Finally, we note that all of these agents other than levofloxacin, ceftriaxone, ertapenem, and plazomicin have every six hour or every eight-hour dosing schedules, and so if given with on-label dosing could require the excess costs of extended hospitalization or nursing facility stay, likely in the several thousands to ten thousands of dollars range.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ **No included studies**	NA	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ **No included studies**	NA	

Other considerations

Acceptability / Stewardship

Is the intervention acceptable to key stakeholders?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ **Varies**	In light of antibiotic stewardship principles (i.e., "coordinated interventions designed to improve and measure the appropriate use of [antibiotic] agents by promoting the selection of the optimal [antibiotic] drug regimen including dosing, duration of therapy, and route of administration" [per IDSA guidelines]), we advocate for the appropriate use of more narrow-spectrum antibiotics in patients without specific risk factors for infection caused by resistant pathogens. One meta-analysis reported that the incidence of *C. difficile* infection could be reduced by lowering exposure to 'high-risk' antibiotics, defined as clindamycin, fluoroquinolones, and cephalosporins, monobactams, and carbapenems .[1] For empiric treatment of cUTI, avoidance of antibiotics with a broad spectrum of activity when an agent with narrower spectrum of activity may be appropriate is aligned with principles of antibiotic stewardship. Empiric antibiotic choice always involves weighing antibiotic stewardship concerns versus the risk of inappropriate initial antibiotic choice.	The panel agrees to classify newer antibiotics as alternative therapies (rather than a preferred therapies) due to stewardship concerns.
Feasibility Is the intervention feasible to implement?		
JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ **Varies**		The panel agrees that resources required in different settings will directly impact feasibility.
Equity What would be the impact on health equity?		
JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ **Varies**		The panel agrees that resources required in different settings will directly impact equity.

1. Brown KA, Khanafer N, Daneman N, Fisman DN. Meta-analysis of antibiotics and the risk of community-associated Clostridium difficile infection. Antimicrob Agents Chemother. 2013 May;57(5):2326-32. doi: 10.1128/AAC.02176-12. Epub 2013 Mar 11. PMID: 23478961; PMCID: PMC3632900.