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

Supplementary material for Duration of Antibiotics for Complicated UTI

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A) For all complicated UTI

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

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
8. duration*
9. “long course” OR “long courses”
10. “short course” OR “short courses”
11. “day course” OR “day regimen”
12. drug administration schedule[MeSH Terms]
13. time factors[MeSH Terms]
14. 8 OR 9 OR 10 OR 11 OR 12 OR 13
15. antibiotic*
16. antimicrobial*
17. antibacterial*
18. anti-bacterial agents[MeSH Terms]
19. 15 OR 16 OR 17 OR 18
20. 14 AND 19
21. 7 AND 20
22. “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]
23. 21 AND 22
24. "2000"[Date - Publication] : "3000"[Date - Publication]
25. 23 AND 24
26. "english"[Language]
27. 25 AND 26

Embase

1. 'cystitis'/exp OR cystitis
2. 'urinary tract infection'/exp OR 'urinary tract infection' OR 'urinary tract infections'
3. 'pyelonephritis'/exp OR pyelonephritis
4. 1 OR 2 OR 3
5. 'time factor'/exp
6. 'drug administration'/exp
7. duration*

8. 'long course' OR 'long courses'
9. 'short course' OR 'short courses'
10. 'day course' OR 'day regimen'
11. 'short term' OR 'long term'
12. 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11
13. 'antiinfective agent'/exp
14. 'antiinfective agent'
15. antibiotic*
16. antimicrobial*
17. antibacterial*
18. 13 OR 14 OR 15 OR 16 OR 17
19. 12 AND 18
20. 4 AND 19
21. 'clinical trial'/de OR 'controlled clinical trial'/de OR 'phase 2 clinical trial'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial' OR 'clinical trial'
22. 20 AND 21
23. 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
24. 22 AND 23
25. english:la
26. 24 AND 25

Cochrane

1. MeSH descriptor: [Cystitis] explode all trees
2. MeSH descriptor: [Urinary Tract Infections] explode all trees
3. MeSH descriptor: [Pyelonephritis] explode all trees
4. cystitis
5. pyelonephritis
6. "urinary tract infection" OR "urinary tract infections"
7. #1 OR #2 OR #3 OR #4 OR #5 OR #6
8. duration*
9. “long course” OR “long courses”
10. "short course" OR "short courses"
11. “day course” OR “day regimen”
12. MeSH descriptor: [Drug Administration Schedule] explode all trees
13. MeSH descriptor: [Time Factors] explode all trees
14. #8 OR #9 OR #10 OR #11 OR #12 OR #13
15. antibiotic*
16. antimicrobial*
17. antibacterial*
18. MeSH descriptor: [Anti-Bacterial Agents] explode all trees
19. #15 OR #16 OR #17 OR #18

20. #14 AND #19
21. #7 AND #20

Eligibility criteria for selection of studies

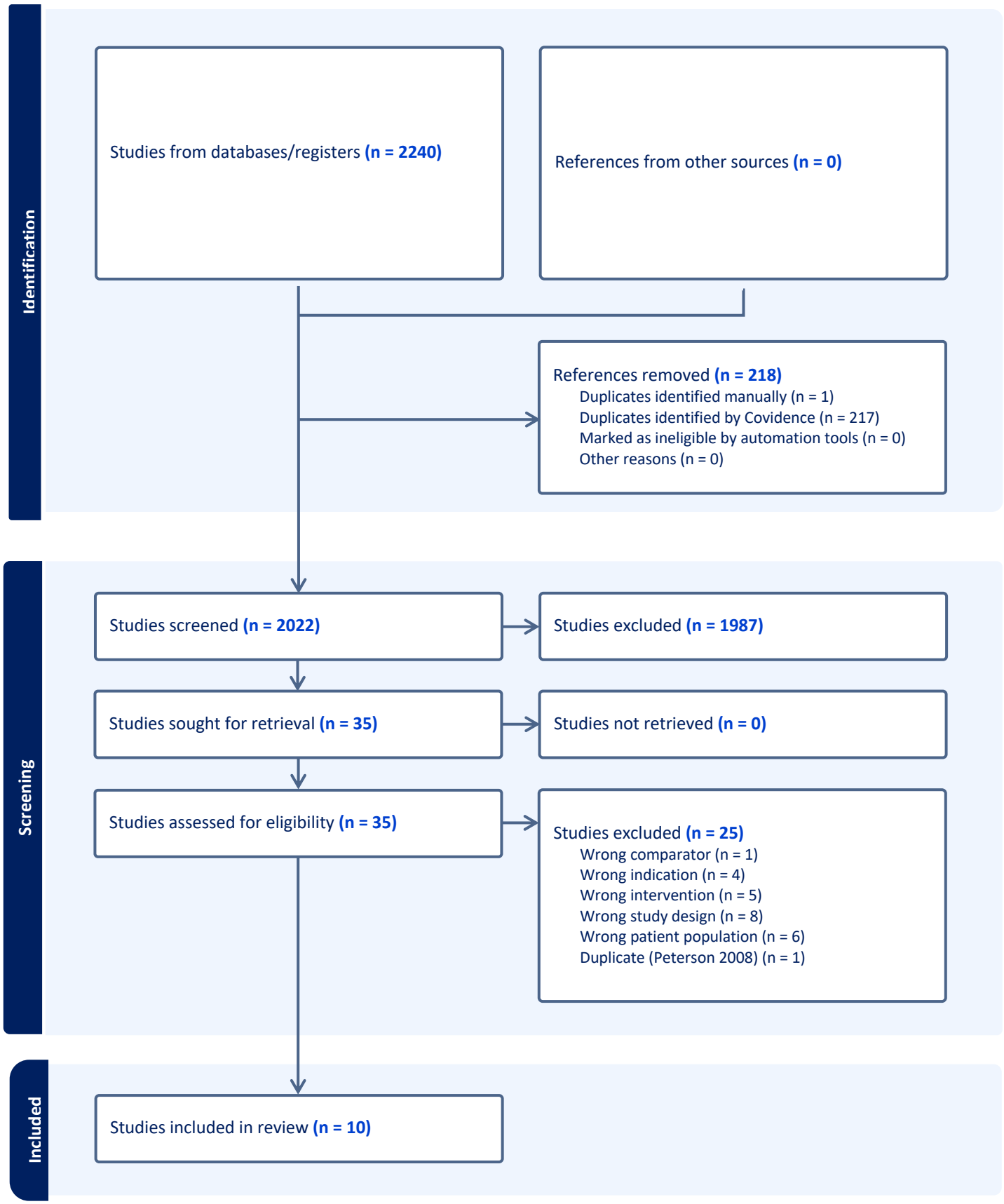
Inclusion criteria:

- Patient population: Adults patients being treated parenterally for cUTI (with or without bacteriemia)
- Intervention:
    - -Total duration of antibiotics between 5 to 7 days
- Comparator:
    - -Total duration of antibiotics between 10 to 14 days
- -Outcomes
    - -Minimally including clinical cure (at TOC)
- Study design: Randomized controlled trials (RCTs)
- 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
- -Intervention / Comparator = supporting indirect evidence only
    - - Total duration of antibiotics either shorter than 5 or longer than 14 days
- -Outcomes
    - -Not including clinical cure (at TOC)

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



Supplementary Table 1: GRADE Evidence profile

Question: In patients presenting with complicated UTI, should total duration of antibiotics be **shorter (<=7 days)** rather than **prolonged to >7 days**?

P: In patients presenting with complicated UTI
I: shorter total duration of antibiotics (<=7 days)
C: prolonged total duration of antibiotics (>7 days)
Setting: Inpatient and Outpatient

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Shorter duration of Abx (5 to 7 days)	Prolonged duration of Abx (10 to 14 days)	Relative (95% CI)	Absolute (95% CI)		
Clinical cure (at Test-of-Cure (TOC))												
10[1-10]	randomised trials	serious[a]	not serious[b]	not serious	not serious[c]	none	903/1014 (89.1%)	962/1096 (87.8%)	**RR 1.00** (0.97 to 1.04)	**0 fewer per 1,000** (from 26 fewer to 35 more)	⊕⊕⊕◯ Moderate	CRITICAL
Microbiological cure (at Test-of-Cure (TOC))												
10[1-10]	randomised trials	serious[d]	not serious[b]	serious[e]	not serious[c]	none	778/915 (85.0%)	824/975 (84.5%)	**RR 0.99** (0.94 to 1.05)	**8 fewer per 1,000** (from 51 fewer to 42 more)	⊕⊕◯◯ Low	IMPORTANT
Recurrence of Infection (up to 180 days)												
6[1,3,5,7,9,10]	randomised trials	serious[a]	not serious[f]	not serious	not serious[c]	none	41/535 (7.7%)	38/548 (6.9%)	**RR 1.07** (0.69 to 1.65)	**5 more per 1,000** (from 21 fewer to 45 more)	⊕⊕⊕◯ Moderate	CRITICAL
Length of hospital stay (median days)												
1[9]	randomised trials	serious[g]	not serious	serious[h]	serious[i]	none	Median: 8 (IQR: 7 to 10) days (n=27)	Median: 14 (IQR 14 to 14.5) days (n=27)	-	median **6 days fewer (p<0.001)**	⊕◯◯◯ Very low	IMPORTANT
Readmission / Rehospitalisation (30 to 90 days)												
3[5,9,10]	randomised trials	serious[g]	not serious	not serious	serious[j]	none	1/236 (0.4%)	1/246 (0.4%)	**RR 0.99** (0.10 to 9.33)	**0 fewer per 1,000** (from 4 fewer to 34 more)	⊕⊕◯◯ Low	IMPORTANT
Serious adverse events (up to 180 days)												
10[1-10]	randomised trials	serious[a]	not serious	not serious	serious[k]	none	38/1370 (2.8%)	52/1478 (3.5%)	**RR 0.82** (0.54 to 1.25)	**6 fewer per 1,000** (from 16 fewer to 9 more)	⊕⊕◯◯ Low	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Shorter duration of Abx (5 to 7 days)	Prolonged duration of Abx (10 to 14 days)	Relative (95% CI)	Absolute (95% CI)		
Non-serious adverse events (up to 180 days)												
8[1,3,4,6-10]	randomised trials	serious[a]	not serious	not serious	serious[k]	none	319/1230 (25.9%)	378/1330 (28.4%)	**RR 0.92** (0.79 to 1.07)	**23 fewer per 1,000** (from 60 fewer to 20 more)	⨁⨁◯◯ Low	IMPORTANT

Notes:
CI: confidence interval; **RR:** risk ratio; **Abx**: antibiotics; **IQR**: interquartile range.

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. Unblinded studies in which the measured outcomes require judgment (e.g., such as how investigators judge clinical improvement or decide to stop the treatment in patients with side effects) were judged to be at risk of high risk of bias. Multiple studies might have been influenced by incomplete outcome data (such as potential attrition bias due to early withdrawal secondary to the lack of diagnostic confirmation and/or frequent late withdrawal), but the extent of this bias was not assessable. Studies funded by industry might also have been biased due to financial conflict of interest. One study showed evidence of failed randomization potentially due to early stoppage of enrollment as well as significant and asymmetrical lost-to-follow up for recurrence of infection (Lafaurie 2023). Outcome measurement time frames varied between studies, with some studies measuring outcomes at an early specific time point after randomization rather than after end of treatment which may bias the assessment in favor of longer duration regimen. These studies were not rated down for risk of bias since this potential bias in favor of the longer course does not lower our confidence in the estimate that shorter is non-inferior to longer).
b. Talan 2000: heterogenous size of effect presented as compared to other studies and no overlapping of the 95% CI interval with at least one study. After removing this study from the analysis, Talan 2000 is clearly the main source of heterogeneity (p-value for heterogeneity: NS and the I-square: 0%). Exploration of the potential sources of heterogeneity show that the comparator was 14 days of TMP-SMX to which 18.3% of uropathogens were resistant to. This could clearly affect the clinical cure at TOC and could explain the variation in size of effect (thus, not rated down for inconsistency).
c. Based on an inferiority margin of 10%, not rated down for imprecision.
d. Multiple studies might have been influenced by incomplete outcome data (such as potential attrition bias due to early withdrawal secondary to the lack of diagnostic confirmation and/or frequent late withdrawal), but the extent of this bias was not assessable. Studies funded by industry might also have been biased due to financial conflict of interest. One study showed evidence of failed randomisation potentially due to early stoppage of enrollment (Lafaurie 2023).
e. Microbiological cure is considered a potential surrogate marker of clinical cure and recurrence of infection, but uncertainty remains around the strength of this association.
f. Darouiche 2014: heterogenous size of effect presented as compared to the other studies but only contributed for 0.8% of the weight (thus, not rated down for inconsistency)
g. Unblinded study which can affect the outcome of interest that require judgment, such as how investigators judge clinical improvement and associated downstream consequences.
h. Rated down for indirectness since length of hospitalization was likely influenced by the route of administration of antimicrobials (all patients received parenteral antibiotics throughout each study for the assigned duration in the hospital, without switching to an oral option) (Rudrabhatla 2018).
i. Small sample size suggests the potential for fragility in the estimate, making the estimate uncertain.
j. Very few events and small sample size. 95% CI may not include a meaningful difference (i.e. crossing the null value), thus the treatment with shorter duration failed to show or exclude a beneficial effect.
k. 95% CI may not include a meaningful difference (i.e. crossing the null value), thus the treatment with shorter duration failed to show or exclude a beneficial effect.

References

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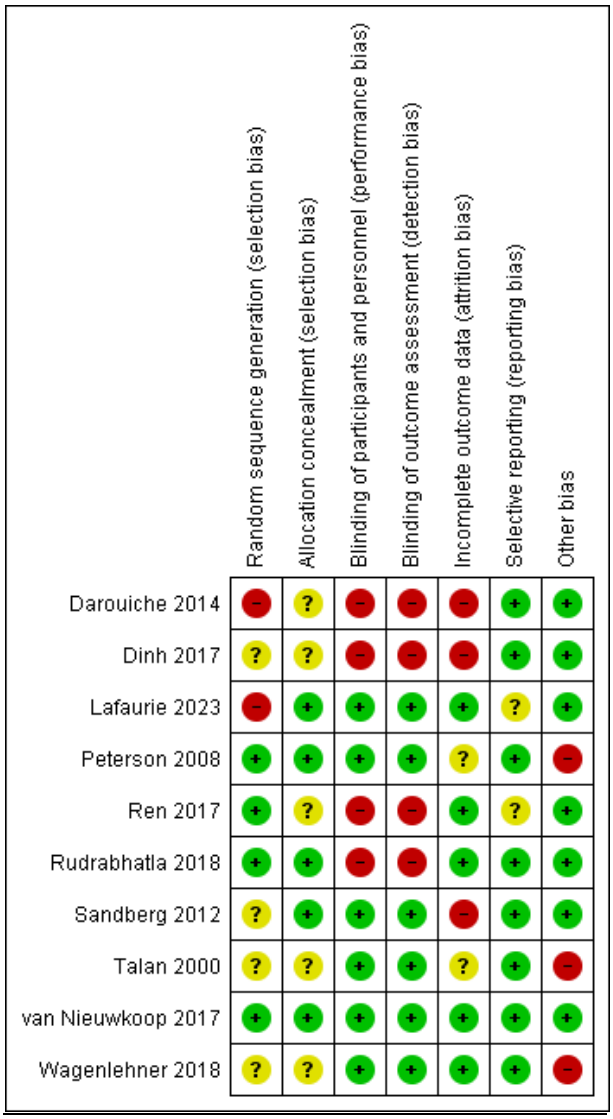
Supplementary Table 2: Characteristics of the included studies (n=10, 2000-2024)

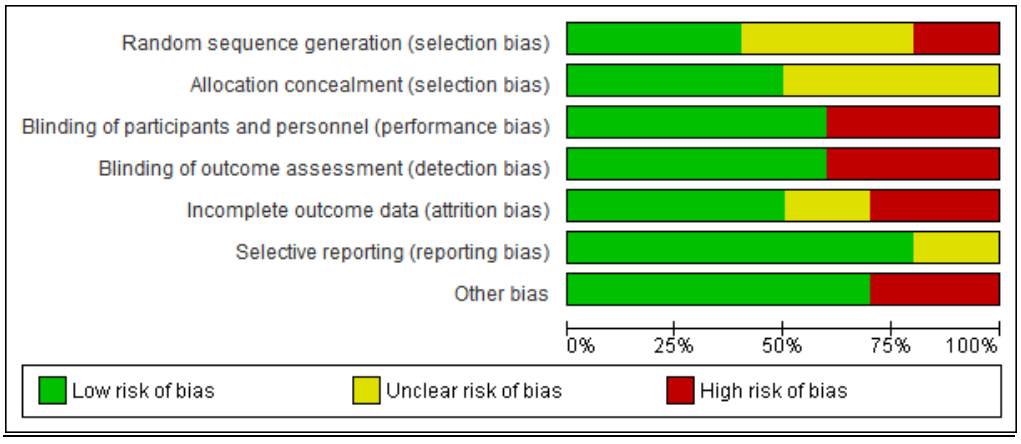
Study *(Lead author, Year of publication, Name of trial, Countries)*	**Population** *(Type UTI, Year of enrollment, N randomised, F (%), Age in Intervention vs Comparator groups)*	**Study design** *(Non-inferiority margin if applicable, primary outcome with its timing)*	**Main uro-pathogens** (*% of resistance)*	**Randomisation** *(timing, and criteria for clinical response if reported)*	**Intervention** *(total duration for shorter courses, IV and oral antibiotics)*	**Comparator** *(total duration for longer courses, IV and oral antibiotics)*
Darouiche 2014 USA	Catheter-related UTI in hospitalised patients with SCI 2007-2011 N= 61 F: 5.5% A (mean): 61.5 vs 58.3y	Non-inferiority trial Margin of 10% for CC at EOT	Mixed (64%)	Based on a presumptive clinical and microbiological diagnosis of catheter-related UTI	5 days (appropriate IV or PO systemic antibiotics, with catheter exchange)	10 days (appropriate IV or PO systemic antibiotics, with catheter retention)
Dinh 2017 France (multicentric)	Uncomplicated AP attending ED 2009-2011 N= 88 F: 100% A (mean): 30.5 vs 33.1y	Non-inferiority trial Margin (NR) for CC at day 30 after EOT	*E. coli* (98%) R to FQ: 0%, since excluded after randomisation	Within 24h of initiation of antibiotic treatment	5 days (PO ofloxacin or levofloxacin)	10 days (PO ofloxacin or levofloxacin)
Lafaurie 2023 PROSTASHORT France (multicentric)	Febrile UTI 2015-2019 N= 240 F: 0% Age (median): 62.3 vs 58.9y	Non-inferiority trial Margin of 10% for treatment success (CC, MC and no new antibiotics) at week 6	*E. coli* (8%) R to FQ: 0%, since exclusion criteria	Three to four days after initiation of antibiotic treatment if afebrile with empirical therapy	7 days (ofloxacin, ceftriaxone or cefotaxime for maximum of 3 days, then switch to PO ofloxacin)	14 days (ofloxacin, ceftriaxone or cefotaxime for maximum of 3 days, then switch to PO ofloxacin)
Peterson 2008 USA (multicentric)	AP/ cUTI 2005-2006 N=1,109 F: 60.9% A (mean): 54.2y (whole cohort)	Non-inferiority trial Margin of 15% for MC at day 15 to 19 after blinded EOT	*E. coli* (86%) R to ciprofloxacin: 9% and levofloxacin: 5%	Based on a clinical and microbiological diagnosis of AP/ cUTI	5 days (IV or PO levofloxacin)	10 days (IV or PO ciprofloxacin)
Ren 2017 China (multicentric)	AP/ cUTI 2012-2014 N= 317 F: 85.2% A (mean): 49.1 vs 50.2y	Non-inferiority trial Margin of 15% % for CC at EOT	*E. coli* (37%) R to FQ: NR	Based on presumptive clinical diagnosis of AP/ cUTI	5 days (IV levofloxacin)	7 to 14 days (IV x 5 days then PO levofloxacin)
Rudrabhatla 2018	AP in hospitalised patients	Non-inferiority trial	*E. coli* (87%)	On day 7 of effective antibiotic regimen (either	7 days	14 days

India	2015-2016 N= 54 F: 58.8% A (median): 51vs 55y	Margin of 15% for retreatment for recurrent UTI at 6 weeks after EOT	R to FQ: 78% (36/46)	empirical or revised), if sustained clinical improvement	(effective non-fluoroquinolone, of which the great majority were aminoglycosides -based regimen)	(effective non-fluoroquinolone, of which the great majority were aminoglycosides -based regimen)
Sandberg 2012 Sweden (multicentric)	AP 2006-2008 N= 248 F:100% A (median): 46 vs 41y	Non-inferiority trial Margin of 10% for CC and MC 10 to 14 days after EOT	*E. coli* (92%) R to FQ: 0%, since excluded after randomisation	Based on presumptive clinical diagnosis of AP	7 days (initial IV as needed, then PO ciprofloxacin)	14 days (initial IV as needed, then PO ciprofloxacin)
Talan 2000 USA (multicentric)	Uncomplicated AP in outpatients 1994-1997 N =378 F: 100% A (median): 25 vs 23y	Non-inferiority trial Margin of 10% for CC and MC at 4 to 11 days after EOT	*E. coli* (68%) R to FQ:0% (1/255) R to TPM-SMX: 18% (47/255)	Within 24h of initiation of antibiotic treatment	7 days (IV X 1 dose if needed, then oral ciprofloxacin)	14 days (IV ceftriaxone X 1 dose if needed, then oral TMP-SMX)
van Nieuwkoop 2017 FUTIRST Netherlands (multicentric)	Febrile UTI 2008-2013 N= 200 F: 57.0% A: 60 vs 61y	Non-inferiority trial Margin of 10% for CC at 10 to 18 days after EOT	*E. coli* (68%) R to FQ: 0%, since exclusion criteria	Three to four days after inclusion (pending results of urine culture)	7 days (ciprofloxacin or b-lactams +/- IV gentamicin, then early switch to PO ciprofloxacin)	14 days (ciprofloxacin or b-lactams +/- IV gentamicin, then early switch to PO ciprofloxacin)
Wagenlehner 2018 Germany and Poland	AP/ cUTI in hospitalised patients 2012-2014 N = 225 F: 82.1% A (group): mostly between 36-65y	Phase II, Descriptive trial CC and MC at TOC (day 17)	*E. coli* (83%) R to FQ: 16% (37/225)	Based on presumptive clinical diagnosis of AP/ cUTI	5 days (IV or PO finafloxacin)	10 days (IV or PO finafloxacin or ciprofloxacin)

UTI=Urinary Tract Infection; cUTI=Complicated UTI; AP=acute pyelonephritis; SCI=spinal cord injury; ED=Emergency department; F=female; y=years; NR=not reported.
CC=clinical cure or response; MC=microbiologic cure, eradication, or response; EOT=end of therapy; TOC=test of cure.
R=resistant, including non-susceptible; S=susceptible; FQ=fluoroquinolone; IV=parenteral; PO=oral.

Supplementary Figure 2: Summary of the Risk of Bias of included studies (Cochrane Risk of Bias tool (n=10)





Supplementary Table 3: Assessment of the Risk of Bias of included studies (Cochrane Risk of bias Tool) (n=10)

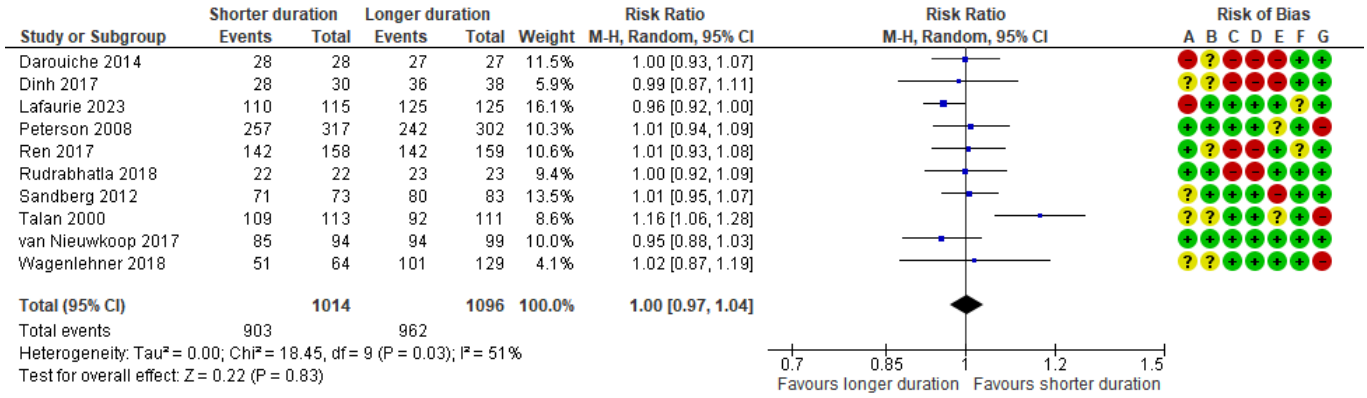
Study *(Lead author, Year of publication, Name of trial, Countries)*	**Random sequence generation** (selection bias)	**Allocation concealment** (selection bias)	**Blinding of participants and personnel** (performance bias)	**Blinding of outcome assessment** (detection bias)	**Incomplete outcome data** (attrition bias)	**Selective reporting** (reporting bias)	**Other bias** (e.g. sources of funding)
Darouiche 2014 USA	High RoB -Computer-generated randomization schedule with randomly permuted blocks -Probable failed randomization: short duration group tended to have more bacteremia at baseline and empirical / definitive choice of antibiotics varied greatly between the 2 groups (comparison most likely underpowered)	Unclear RoB -Not reported	High RoB -Open-label (especially applicable to subjective outcomes)	High RoB -Open-label (especially applicable to subjective outcomes)	High RoB -Early withdrawal after randomisation (for bacteremia) occurred exclusively in the short duration group	Low RoB	Low RoB -Not industry-funded -No financial relationship disclosed by authors
Dinh 2017 France (multicentric)	Unclear RoB -Randomization (not further detailed) -Comparable patients' characteristics at baseline, except for a trend towards higher CRP in short duration group	Unclear RoB -Not reported	High RoB -Open-label (especially applicable to subjective outcomes)	High RoB -Open-label (especially applicable to subjective outcomes)	High RoB -Early withdrawal after randomisation (for absence of uropathogen or FQ-resistance uropathogen) lead to premature stoppage of the trial for safety reasons (10% FQ-resistance)	Low RoB	Low RoB -Not industry-funded -No conflict of interest declared by authors
Lafaurie 2023 PROSTA-SHORT France (multicentric)	High RoB -Stratified randomization (by age, urinary tract-related comorbidities and center) with permutation blocks of varying sizes -Probable failed randomization: short duration group had more comorbidities at baseline and more infections caused by *E..coli*	Low RoB -Randomisation via a centralised web-based system	Low RoB -Placebo-controlled	Low RoB -Placebo-controlled	Low to Unclear RoB -No significant lost to follow up at 6 weeks (e.g. clinical failure) -Significant and asymmetrical lost to follow up after 6 weeks (27% vs 17% of lost to follow up in the short vs prolonged duration groups, respectively) (e.g. recurrence of infection) -Asymmetrical timing of outcomes measurement	Unclear RoB -Recurrence of infection at 6 weeks is not reported (but is between 6 and 12 weeks)	Low RoB -Not funded by industry

					potentially favoring longer duration		
Peterson 2008 USA (multicentric)	Low RoB -Computer-generated randomization schedule with randomly permuted blocks -Comparable patients' characteristics at baseline	Low RoB -Randomisation via a central service	Low RoB -Placebo-controlled	Low RoB -Placebo-controlled	Unclear RoB -Early withdrawal after randomisation (if NOT having an appropriate clinical diagnosis of AP or cUTI, a positive urine culture with 1 or 2 uropathogens) was frequent, but symmetrical between groups. No analysis was provided to assess the impact of early withdrawal. -Asymmetrical timing of outcomes measurement (potentially favoring longer duration)	Low RoB	High RoB -Industry-funded: grant related to one the studied molecules (involvement of industry not reported but authors are employees of this specific company)
Ren 2017 China (multicentric)	Low RoB -Randomization (not further detailed) -Comparable patients' characteristics at baseline	Unclear RoB -Not reported	High RoB -Open-label (especially applicable to subjective outcomes)	High RoB -Open-label (especially applicable to subjective outcomes)	Low RoB -All outcomes analysed in the ITT population -No significant lost to follow up	Unclear RoB -Clinical recurrence mentioned in abstract but not reported in manuscript	Low RoB -Funding not reported but no COI disclosed by authors
Rudrabhatla 2018 India	Low RoB -Computer-generated randomization with minimization method to balance prognostic variables (gender, age, comorbidities, regimen received) -Comparable patients' characteristics at baseline	Low RoB -Randomization using a biased-coin method	High RoB -Open-label (especially applicable to subjective outcomes)	High RoB -Open-label (especially applicable to subjective outcomes)	Low RoB -All outcomes analysed in the ITT population -No significant lost to follow up	Low RoB	Low RoB -No funding received and no competing interests declared by authors
Sandberg 2012 Sweden (multicentric)	Unclear RoB -Computer-generated randomization sequence with randomly blocks for each study site -Comparable patients' characteristics at baseline, but comparison most likely underpowered	Low RoB -Randomization via a central service	Low RoB -First week was open-label while the second week was placebo-controlled (especially influencing the route of administration)	Low RoB -First week was open-label while the second week was placebo-controlled (especially influencing the route of administration)	High RoB -Early withdrawal after randomisation (if NOT having an appropriate clinical diagnosis of AP or cUTI, a positive urine culture with 1 or 2 uropathogens susceptible to ciprofloxacin) in addition to lost to follow up was frequent and asymmetrical between groups (42% vs 32% in the short duration group vs the prolonged duration group,	Low RoB	Low RoB -Not industry-funded -Sponsor not involved in study design, collection, analysis and interpretation of data, reviewing the report and the decision to submit the report for publication

					respectively). No analysis was provided to assess the impact of early withdrawal.		
Talan 2000 USA (multicentric)	Unclear RoB -Randomization (not further detailed) -Comparable patients' characteristics at baseline (in efficacy valid groups), except for a trend towards more bacteremia in the prolonged duration group	Unclear RoB -Not reported	Low RoB -Placebo-controlled	Low RoB -Placebo-controlled	Unclear RoB -Early withdrawal after randomisation (if NOT having an appropriate clinical diagnosis of uAP, a positive urine culture with uropathogens) in addition to lost to follow up was frequent and asymmetrical between groups (33% vs 32%). No analysis was provided to assess the impact of early withdrawal.	Low RoB	High RoB -Industry-funded: grant related to one the studied molecules (involvement of industry not reported but authors either received lecture honoraria, research support and/or are employees of this specific company)
van Nieuwkoop 2017 FUTIRST Netherlands (multicentric)	Low RoB -Computer-generated randomization list with permuted blocks -Comparable patients' characteristics at baseline	Low RoB -Randomization via a central service	Low RoB -First week was open-label while the second week was placebo-controlled (especially influencing the route of administration)	Low RoB -First week was open-label while the second week was placebo-controlled (especially influencing the route of administration)	Low RoB -All outcomes analysed in the ITT population -No significant lost to follow up	Low RoB	Low RoB -Not industry-funded -Sponsor not involved in study design, data collection,analysis and interpretation, writing of the report
Wagenlehner 2018 Germany and Poland	Unclear RoB -Randomization (not further detailed) -Comparable patients' characteristics at baseline, but comparison most likely underpowered	Unclear RoB -Not reported	Low RoB -Placebo-controlled	Low RoB -Placebo-controlled	Low RoB -Early withdrawal after randomisation (if NOT having an appropriate clinical diagnosis of AP or cUTI, a positive urine culture with a uropathogen susceptible to the studied drug) was relatively infrequent and symmetrical between groups. -Asymmetrical timing of outcomes measurement (potentially favoring longer duration)	Low RoB	High RoB -Industry-funded: grant related to one the studied molecules (involvement of industry not reported)
RoB=Risk of Bias; cUTI=complicated urinary tract infection; AP= acute pyelonephritis; uAP=uncomplicated AP; FQ=fluoroquinolone; IV=parenteral; ITT=intention-to-treat.							

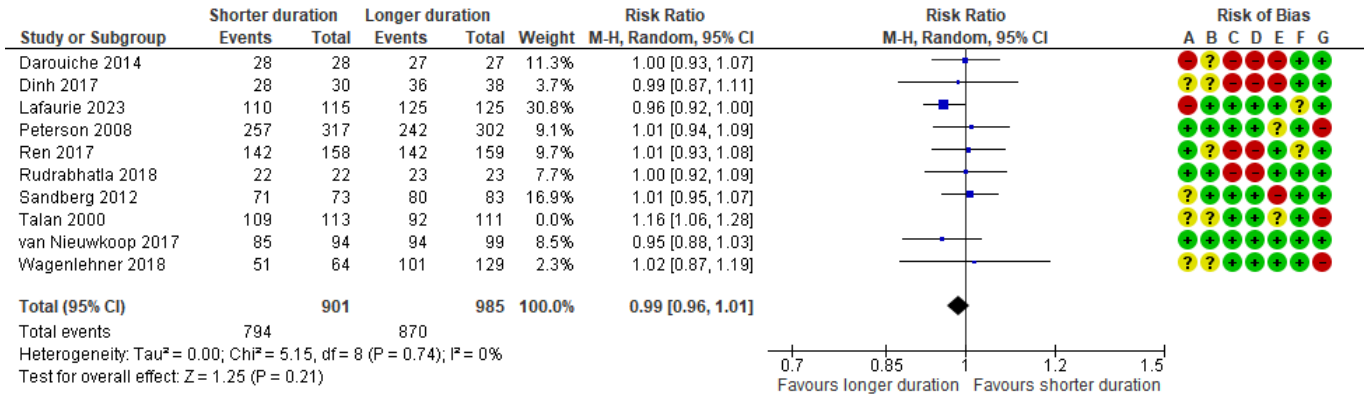
Supplementary Figures 3: Forest plots for each patient-important outcome

3a) 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

3b) Clinical cure (at TOC): *Sensitivity analysis after removing Talan 2000*



Risk of bias legend
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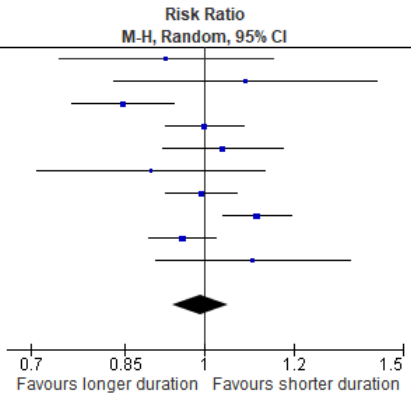
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

3c) Microbiological cure (at TOC)

Study or Subgroup	Shorter duration Events	Total	Longer duration Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Darouiche 2014	23	28	24	27	5.1%	0.92 [0.74, 1.15]
Dinh 2017	20	23	16	20	3.7%	1.09 [0.83, 1.42]
Lafaurie 2023	91	115	117	125	11.8%	0.85 [0.76, 0.94]
Peterson 2008	253	317	241	302	14.1%	1.00 [0.92, 1.08]
Ren 2017	60	67	63	73	10.3%	1.04 [0.92, 1.17]
Rudrabhatla 2018	18	22	21	23	4.6%	0.90 [0.71, 1.13]
Sandberg 2012	69	73	79	83	14.6%	0.99 [0.92, 1.07]
Talan 2000	112	113	90	101	14.9%	1.11 [1.04, 1.19]
van Nieuwkoop 2017	86	93	89	92	15.0%	0.96 [0.89, 1.02]
Wagenlehner 2018	46	64	84	129	5.9%	1.10 [0.90, 1.35]
Total (95% CI)		**915**		**975**	**100.0%**	**0.99 [0.94, 1.05]**
Total events	778		824			

Heterogeneity: Tau² = 0.00; Chi² = 23.47, df = 9 (P = 0.005); I² = 62%
Test for overall effect: Z = 0.28 (P = 0.78)



Risk of bias legend
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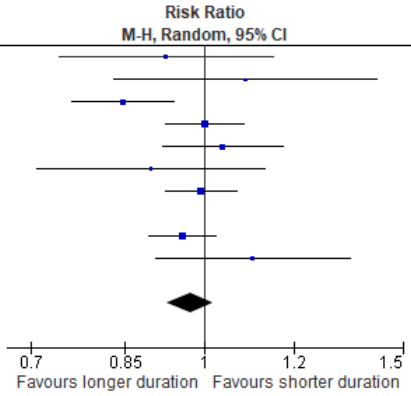
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

3d) Microbiological cure (at TOC): *Sensitivity analysis after removing Talan 2000*

Study or Subgroup	Shorter duration Events	Total	Longer duration Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Darouiche 2014	23	28	24	27	4.3%	0.92 [0.74, 1.15]
Dinh 2017	20	23	16	20	2.9%	1.09 [0.83, 1.42]
Lafaurie 2023	91	115	117	125	13.5%	0.85 [0.76, 0.94]
Peterson 2008	253	317	241	302	18.5%	1.00 [0.92, 1.08]
Ren 2017	60	67	63	73	10.9%	1.04 [0.92, 1.17]
Rudrabhatla 2018	18	22	21	23	3.8%	0.90 [0.71, 1.13]
Sandberg 2012	69	73	79	83	19.9%	0.99 [0.92, 1.07]
Talan 2000	112	113	90	101	0.0%	1.11 [1.04, 1.19]
van Nieuwkoop 2017	86	93	89	92	21.0%	0.96 [0.89, 1.02]
Wagenlehner 2018	46	64	84	129	5.1%	1.10 [0.90, 1.35]
Total (95% CI)		**802**		**874**	**100.0%**	**0.97 [0.93, 1.02]**
Total events	666		734			

Heterogeneity: Tau² = 0.00; Chi² = 12.02, df = 8 (P = 0.15); I² = 33%
Test for overall effect: Z = 1.21 (P = 0.23)



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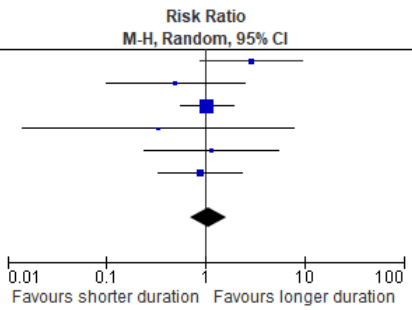
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

3e) Recurrence of infection (up to 180 days)

Study or Subgroup	Shorter duration Events	Total	Longer duration Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Darouiche 2014	9	28	3	27	13.1%	2.89 [0.88, 9.56]
Lafaurie 2023	2	84	5	104	7.2%	0.50 [0.10, 2.49]
Peterson 2008	20	229	18	213	50.5%	1.03 [0.56, 1.90]
Rudrabhatla 2018	0	27	1	27	1.9%	0.33 [0.01, 7.84]
Sandberg 2012	3	73	3	83	7.6%	1.14 [0.24, 5.46]
van Nieuwkoop 2017	7	94	8	94	19.8%	0.88 [0.33, 2.32]
Total (95% CI)		**535**		**548**	**100.0%**	**1.07 [0.69, 1.65]**
Total events	41		38			

Heterogeneity: Tau² = 0.00; Chi² = 4.24, df = 5 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.31 (P = 0.76)



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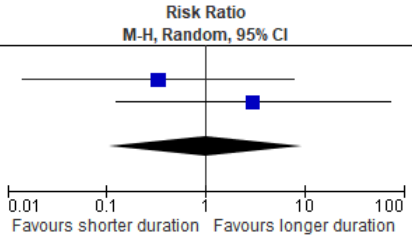
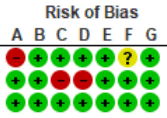
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

3f) Rehospitalisation / Readmission (30 to 90 days)

Study or Subgroup	Shorter duration Events	Total	Longer duration Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Lafaurie 2023	0	115	0	125		Not estimable
Rudrabhatla 2018	0	27	1	27	50.5%	0.33 [0.01, 7.84]
van Nieuwkoop 2017	1	94	0	94	49.5%	3.00 [0.12, 72.72]
Total (95% CI)		**236**		**246**	**100.0%**	**0.99 [0.10, 9.33]**
Total events	1		1			

Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 0.01 (P = 0.99)



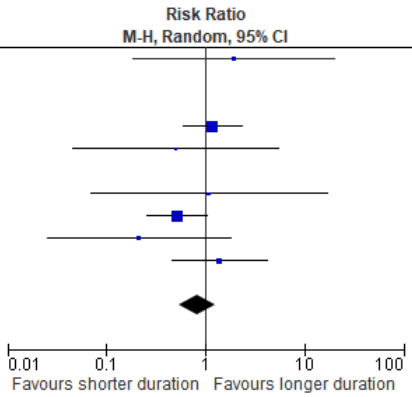


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

3g) Serious Adverse events (up to 180 days)

Study or Subgroup	Shorter duration Events	Total	Longer duration Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Darouiche 2014	2	28	1	27	3.2%	1.93 [0.19, 20.05]
Dinh 2017	0	43	0	45		Not estimable
Lafaurie 2023	0	115	0	125		Not estimable
Peterson 2008	17	543	15	559	37.6%	1.17 [0.59, 2.31]
Ren 2017	1	164	2	165	3.1%	0.50 [0.05, 5.49]
Rudrabhatla 2018	0	27	0	27		Not estimable
Sandberg 2012	1	86	1	93	2.3%	1.08 [0.07, 17.02]
Talan 2000	11	191	21	187	35.8%	0.51 [0.25, 1.03]
van Nieuwkoop 2017	1	97	5	103	3.9%	0.21 [0.03, 1.79]
Wagenlehner 2018	5	76	7	147	14.2%	1.38 [0.45, 4.21]
Total (95% CI)		**1370**		**1478**	**100.0%**	**0.82 [0.54, 1.25]**
Total events	38		52			

Heterogeneity: Tau² = 0.00; Chi² = 5.86, df = 6 (P = 0.44); I² = 0%
Test for overall effect: Z = 0.90 (P = 0.37)

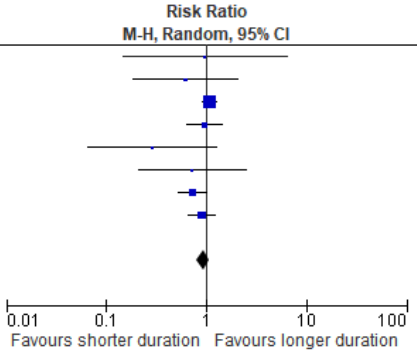


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

3h) Non-Serious adverse events (up to 180 days)

Study or Subgroup	Shorter duration Events	Total	Longer duration Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Darouiche 2014	2	28	2	27	0.6%	0.96 [0.15, 6.37]
Lafaurie 2023	4	115	7	125	1.6%	0.62 [0.19, 2.07]
Peterson 2008	192	543	185	559	45.3%	1.07 [0.91, 1.26]
Ren 2017	36	164	38	165	12.5%	0.95 [0.64, 1.42]
Rudrabhatla 2018	2	27	7	27	1.0%	0.29 [0.07, 1.25]
Sandberg 2012	4	86	6	93	1.5%	0.72 [0.21, 2.47]
Talan 2000	46	191	62	187	17.9%	0.73 [0.53, 1.00]
Wagenlehner 2018	33	76	71	147	19.6%	0.90 [0.66, 1.22]
Total (95% CI)		**1230**		**1330**	**100.0%**	**0.92 [0.79, 1.07]**
Total events	319		378			

Heterogeneity: Tau² = 0.01; Chi² = 7.99, df = 7 (P = 0.33); I² = 12%
Test for overall effect: Z = 1.03 (P = 0.30)



Risk of bias legend
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(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
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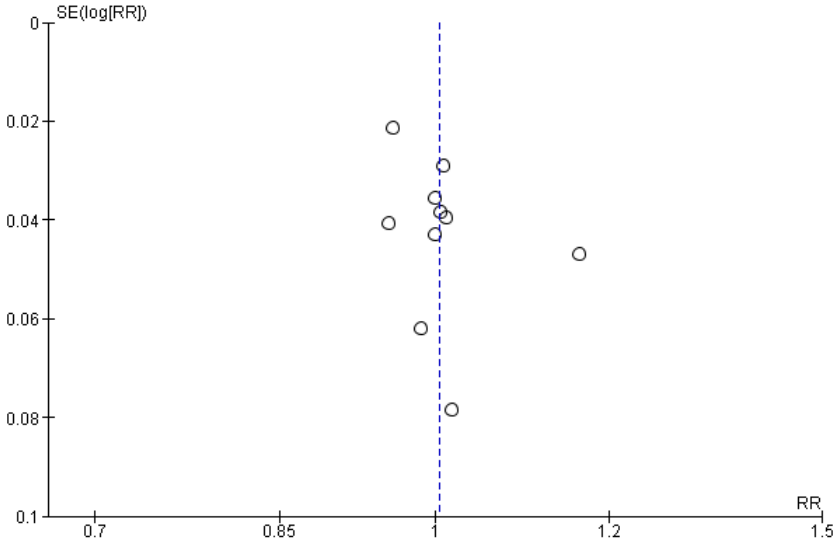
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Supplementary Figure 4: Funnel plot for clinical cure Clinical cure (at Test-of-Cure (TOC))



Supplementary Table 4: GRADE Evidence to Decision framework for all cUTI

Summary of Judgments							
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	No included studies
ACCEPTABILITY / STEWARDSHIP	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	**Increased**	Varies	Don't know

Type of Recommendation				
Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	○	○

B) Stratification for choice of antibiotics

Supplementary Table 5: GRADE Evidence Profile

Question: In patients presenting with complicated UTI **treated with fluoroquinolones**, should total duration of antibiotics be **shorter (<=7 days)** rather than **prolonged to >7 days**?

P: In patients presenting with complicated UTI **treated with fluoroquinolones (FQ)**
I: shorter total duration of antibiotics (<=7 days)
C: prolonged total duration of antibiotics (>7 days)
Setting: Inpatient and Outpatient

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Shorter duration of FQ (5 to 7 days)	Prolonged duration of FQ (10 to 14 days)	Relative (95% CI)	Absolute (95% CI)		
Clinical cure (at Test-of-Cure (TOC))												
7[1-7]	randomised trials	serious[a]	not serious	not serious	not serious[b]	none	744/851 (87.4%)	820/935 (87.7%)	**RR 0.98** (0.96 to 1.01)	**18 fewer per 1,000** (from 35 fewer to 9 more)	⊕⊕⊕◯ Moderate	CRITICAL
Microbiological cure (at TOC)												
7[1-7]	randomised trials	serious[c]	not serious	serious[d]	not serious[b]	none	625/752 (83.1%)	689/824 (83.6%)	**RR 0.98** (0.93 to 1.03)	**17 fewer per 1,000** (from 59 fewer to 25 more)	⊕⊕◯◯ Low	IMPORTANT
Recurrence of Infection (up to 90 days)												
4[1,3,5,7]	randomised trials	serious[a]	not serious	not serious	not serious[b]	none	32/480 (6.7%)	34/494 (6.9%)	**RR 0.94** (0.59 to 1.51)	**4 fewer per 1,000** (from 28 fewer to 35 more)	⊕⊕⊕◯ Moderate	CRITICAL
Readmission / Rehospitalisation (30 to 90 days)												
2[3,7]	randomised trials	serious[e]	not serious	not serious	serious[f]	none	1/209 (0.5%)	0/219 (0.0%)	**RR 3.00** (0.12 to 72.72)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕◯◯ Low	IMPORTANT
Serious adverse events (up to 180 days)												
7[1-7]	randomised trials	serious[a]	not serious	not serious	serious[g]	none	25/1124 (2.2%)	30/1237 (2.4%)	**RR 1.04** (0.61 to 1.78)	**1 more per 1,000** (from 9 fewer to 19 more)	⊕⊕◯◯ Low	IMPORTANT
Non-serious adverse events (up to 180 days)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Shorter duration of FQ (5 to 7 days)	Prolonged duration of FQ (10 to 14 days)	Relative (95% CI)	Absolute (95% CI)		
5[1,4,5,6,7]	randomised trials	serious[a]	not serious	not serious	serious[g]	none	269/964 (27.9%)	307/1089 (28.2%)	**RR 1.01** (0.88 to 1.15)	**3 more per 1,000** (from 34 fewer to 42 more)	⊕⊕◯◯ Low	IMPORTANT

Notes:
Length of hospital stay – this outcome (judged important for decision-making) was not reported.

CI: confidence interval; **RR:** risk ratio; **FQ**: fluoroquinolone

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. Unblinded studies in which the measured outcomes require judgment (e.g., such as how investigators judge clinical improvement or decide to stop the treatment in patients with side effects) were judged to be at risk of high risk of bias. Multiple studies might have been influenced by incomplete outcome data (such as potential attrition bias due to early withdrawal secondary to the lack of diagnostic confirmation and/or frequent late withdrawal), but the extent of this bias was not assessable. Studies funded by industry might also have been biased due to financial conflict of interest. One study showed evidence of failed randomization potentially due to early stoppage of enrollment as well as significant and asymmetrical lost-to-follow up for recurrence of infection (Lafaurie 2023). Outcome measurement time frames varied between studies, with some studies measuring outcomes at an early specific time point after randomization rather than after end of treatment which may bias the assessment in favor of longer duration regimen. These studies were not rated down for risk of bias since this potential bias in favor of the longer course does not lower our confidence in the estimate that shorter is non-inferior to longer).
b. Based on an inferiority margin of 10%, not rated down for imprecision.
c. Multiple studies might have been influenced by incomplete outcome data (such as potential attrition bias due to early withdrawal secondary to the lack of diagnostic confirmation and/or frequent late withdrawal), but the extent of this bias was not assessable. Studies funded by industry might also have been biased due to financial conflict of interest. One study showed evidence of failed randomization potentially due to early stoppage of enrollment as well as significant and asymmetrical lost-to-follow up for recurrence of infection (Lafaurie 2023).
d. Microbiological cure is considered a potential surrogate marker of clinical cure and recurrence of infection, but major uncertainty remains around the strength of this association.
e. Unblinded study which can affect the outcome of interest that require judgment, such as how investigators judge clinical improvement and associated downstream consequences.
f. Very few events and small sample size. 95% CI may not include a meaningful difference (i.e. crossing the null value), thus the treatment with shorter duration failed to show or exclude a beneficial effect.
g. 95% CI may not include a meaningful difference (i.e. crossing the null value), thus the treatment with shorter duration failed to show or exclude a beneficial effect.

References

1.Peterson, J., Kaul, S., Khashab, M., Fisher, A. C., Kahn, J. B.. A double-blind, randomized comparison of levofloxacin 750 mg once-daily for five days with ciprofloxacin 400/500 mg twice-daily for 10 days for the treatment of complicated urinary tract infections and acute pyelonephritis. Urology ; 2008.
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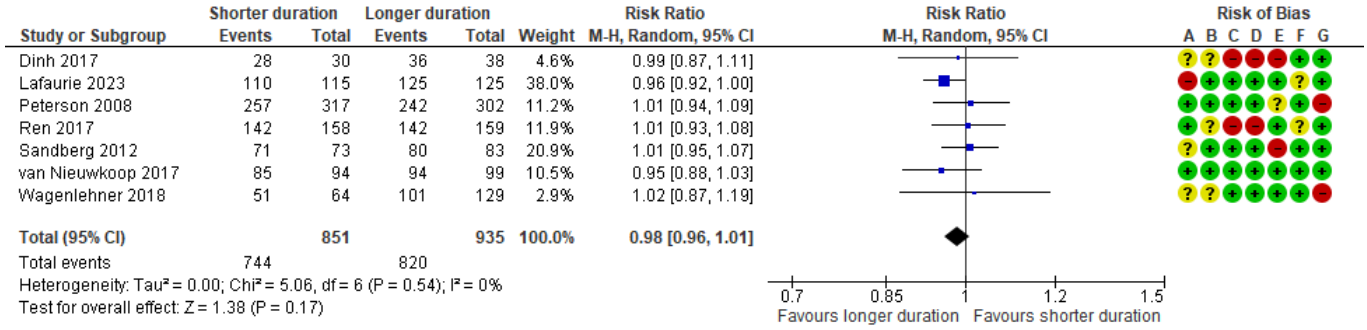
Supplementary Figures 5: Forest plots for each patient-important outcome

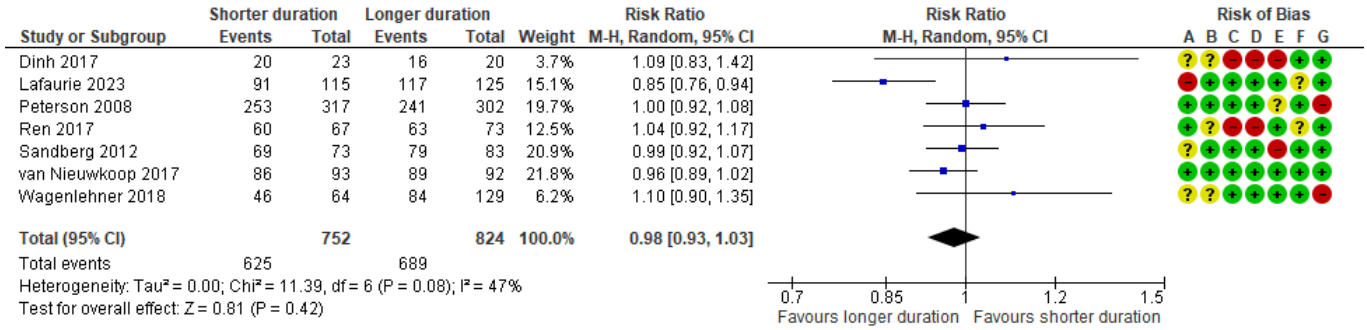
Subgroup analysis: Fluoroquinolones (not including Darouiche 2014, Rudrabhatla 2018 and Talan 2000)

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

5b) Microbiological cure (at TOC)



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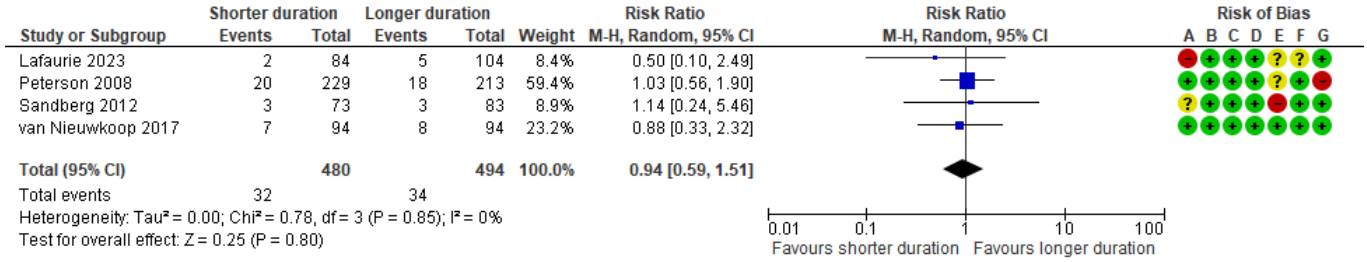
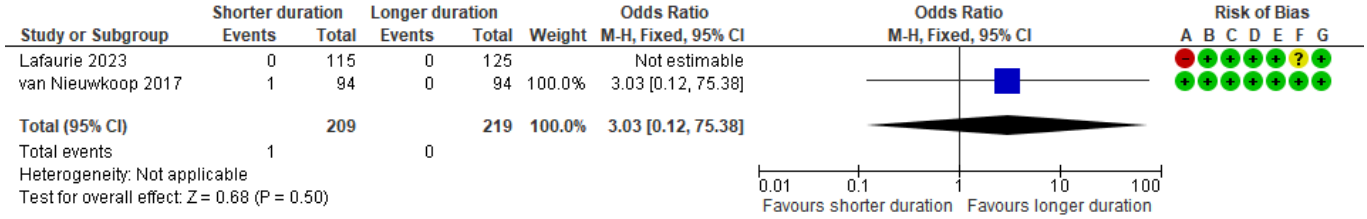
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

5c) Recurrence of infection (up to 90 days)



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

5d) Rehospitalisation / Readmission (30 to 90 days)

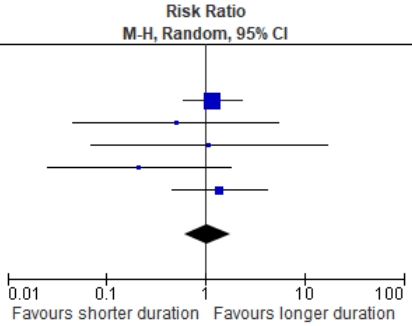


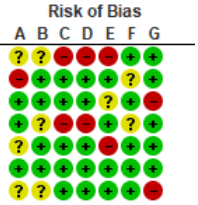
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

5e) Serious Adverse events (up to 180 days)

Study or Subgroup	Shorter duration Events	Total	Longer duration Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Dinh 2017	0	43	0	45		Not estimable
Lafaurie 2023	0	115	0	125		Not estimable
Peterson 2008	17	543	15	559	61.6%	1.17 [0.59, 2.31]
Ren 2017	1	164	2	165	5.0%	0.50 [0.05, 5.49]
Sandberg 2012	1	86	1	93	3.8%	1.08 [0.07, 17.02]
van Nieuwkoop 2017	1	97	5	103	6.4%	0.21 [0.03, 1.79]
Wagenlehner 2018	5	76	7	147	23.2%	1.38 [0.45, 4.21]
Total (95% CI)		**1124**		**1237**	**100.0%**	**1.04 [0.61, 1.78]**
Total events	25		30			

Heterogeneity: Tau² = 0.00; Chi² = 2.89, df = 4 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.15 (P = 0.88)



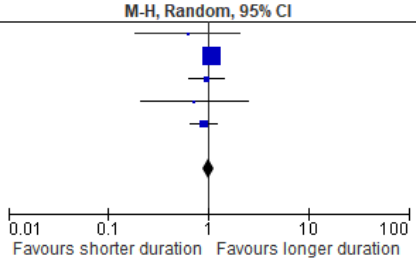


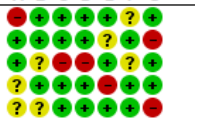
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

5f) Non-Serious adverse events (up to 180 days)

Study or Subgroup	Shorter duration Events	Total	Longer duration Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Lafaurie 2023	4	115	7	125	1.2%	0.62 [0.19, 2.07]
Peterson 2008	192	543	185	559	67.2%	1.07 [0.91, 1.26]
Ren 2017	36	164	38	165	11.2%	0.95 [0.64, 1.42]
Sandberg 2012	4	86	6	93	1.2%	0.72 [0.21, 2.47]
Wagenlehner 2018	33	76	71	147	19.2%	0.90 [0.66, 1.22]
Total (95% CI)		**984**		**1089**	**100.0%**	**1.01 [0.88, 1.15]**
Total events	269		307			

Heterogeneity: Tau² = 0.00; Chi² = 2.01, df = 4 (P = 0.73); I² = 0%
Test for overall effect: Z = 0.13 (P = 0.90)

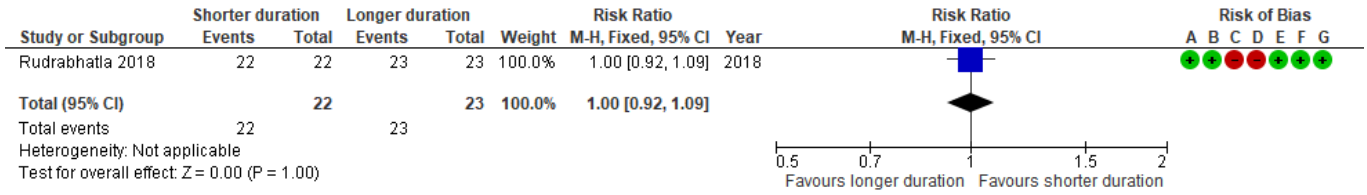




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

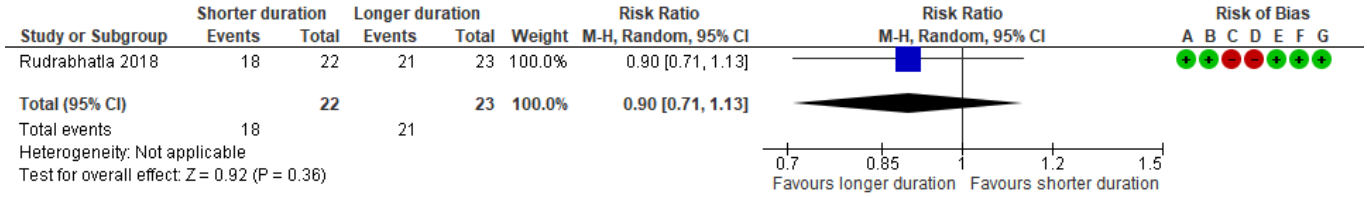
Subgroup analysis: Non-Fluoroquinolones (including Rudrabhatla 2018)

5g) Clinical cure (at Test-of-Cure (TOC))



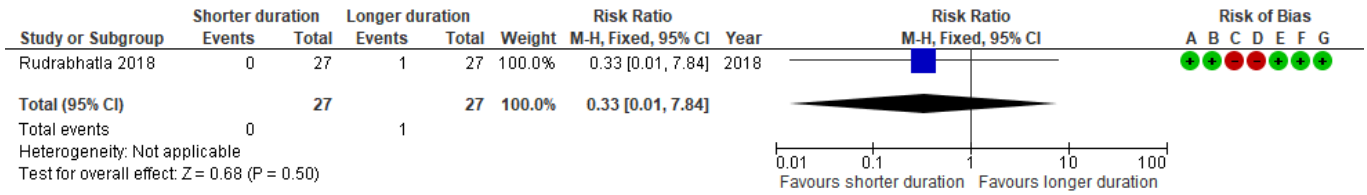
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

5h) Microbiological cure (at TOC)



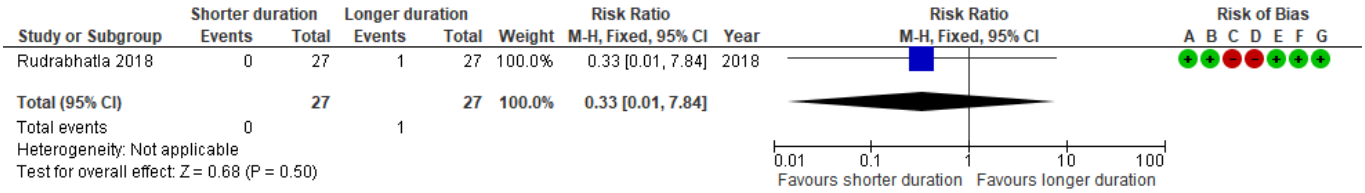
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

5i) Recurrence of infection (at 6-8 weeks)



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

5j) Rehospitalisation / Readmission (up to 6 weeks)

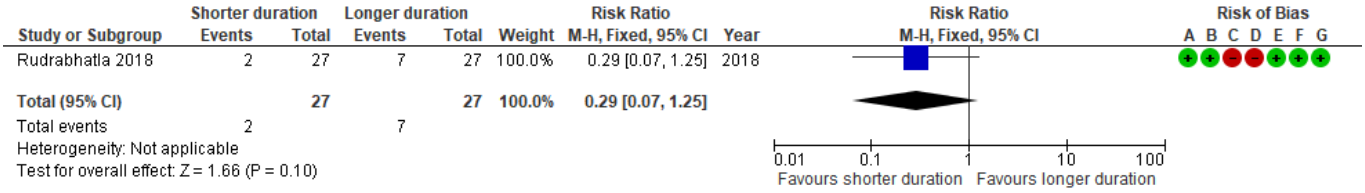


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

5k) Serious Adverse events (up to 6 weeks)

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

5l) Non-Serious adverse events (up to 6 weeks)



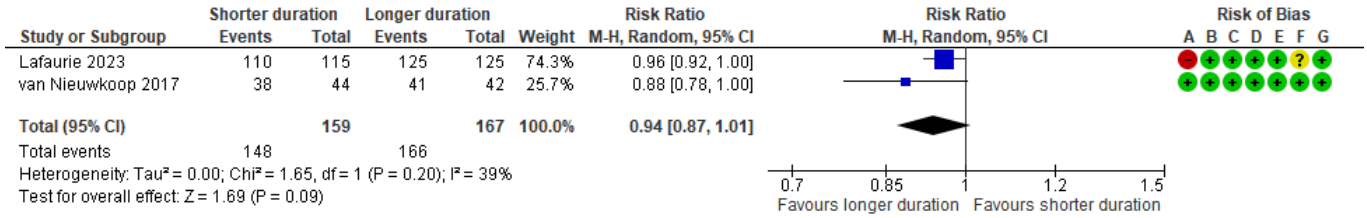
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

C) Stratification for gender

Subgroup analysis: Males (including Lafaurie 2023 and post hoc analysis of Niewkoop 2017)

Supplementary Figures 6: Forest plots for each patient-important outcome

6a) 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)
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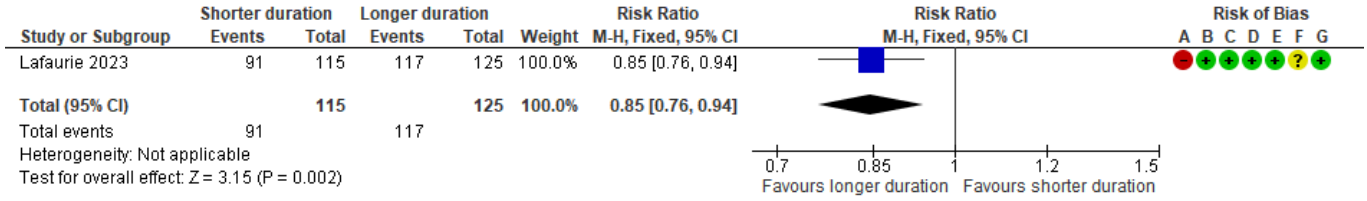
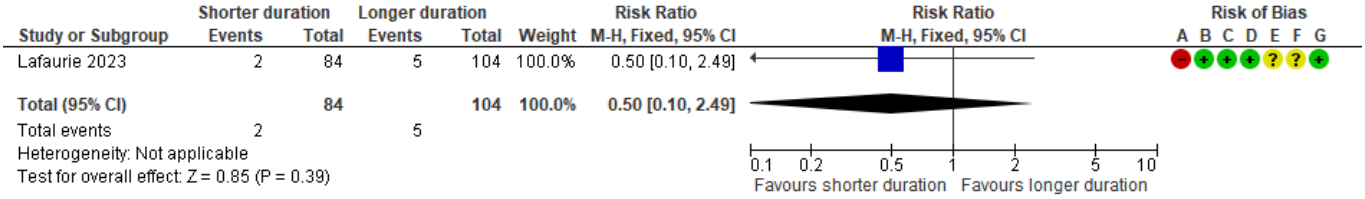
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

6b) 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

6c) Recurrence of infection (at 6-12 weeks)

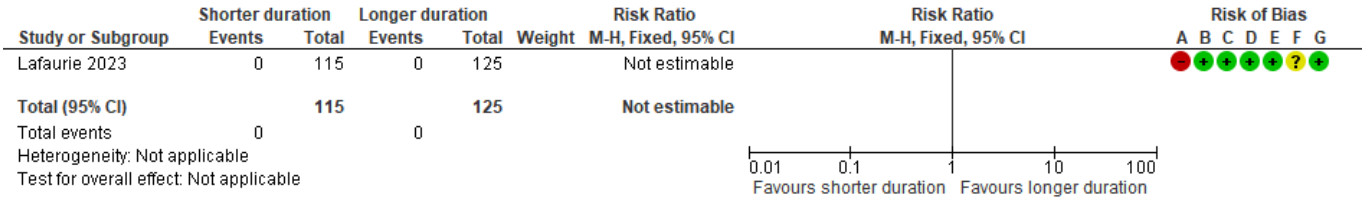


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

6d) Readmission/ Rehospitalisation (up to 6-12 weeks) **Data from personal communication with authors*

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

6e) Serious adverse events (up to 6 weeks)



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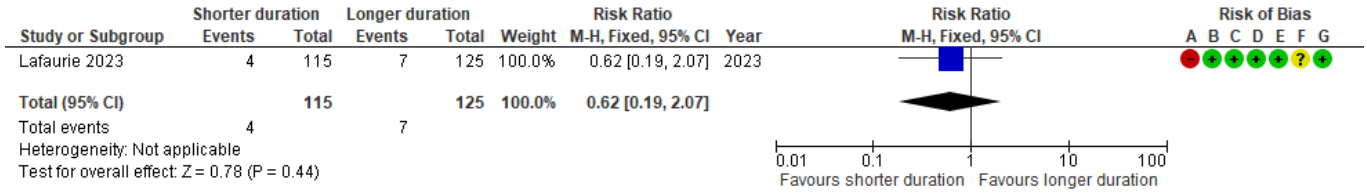
(F) Selective reporting (reporting bias)
(G) Other bias

6f) Non-serious adverse events (up to 6 weeks)



Risk of bias legend
(**A**) Random sequence generation (selection bias)
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(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Subgroup analysis: Eligibility criteria of each individual study for enrolling men (presence/absence of acute bacterial prostatitis)

Supplementary Table 6: Studies of duration of treatment for cUTI including men showing impact of prostatitis on treatment effectiveness (n=7, 2000-2024) (see main text for Forest plot of these 7 trials)

Study *(Lead author, Year of publication, Name of trial, Countries)*	**Males included** *(No, %)*	**Exclusion / Inclusion criteria-based on presence/ absence of involvement of prostate/ epididymis**	**Stratified analysis for male with/without prostatitis**	**Relative estimate of clinical cure in the whole population**	**Relative estimate of clinical cure in men**	**Relative estimate of clinical cure in men with suspected acute bacterial prostatitis**
Peterson 2008 USA (multicentric)	**427 (39%)**	Excluded if presence of acute bacterial prostatitis or epididymitis	NR	RR 1.05 (0.97-1.14)	NA	NA
Rudrabhatla 2018 India	24 (41%)	Excluded if evidence of prostatitis or prostatic abscess	NR	RR 1.00 (0.92 to 1.09)	NA	NA
Darouiche 2014 USA	52 (95%)	NR	NR	RR 1.00 (0.93 to 1.07)	Likely very similar to the whole population	NA
Ren 2017 China (multicentric)	40 (15%)	NR	NR	RR 1.01 (0.93 to 1.08)	NA	NA
Wagenlehner 2018 Germany and Poland	40 (18%)	NR	NR	RR 1.09 (0.96 to 1.23)	NA	NA
Lafaurie 2023 PROSTA-SHORT France (multicentric)	240 (100%)	Males with acute prostatitis included. Acute prostatitis was diagnosed based on pain on rectal examination, which was not systematically performed	Post-hoc analysis presence / absence of pain on rectal examination	RR 0.96 (0.92 to 1.00)	RR 0.96 (0.92 to 1.00)	In a subset of 27 men with pain on rectal examination, RR 0.77 (0.49 to 1.20) *
van Nieuwkoop 2017 FUTIRST Netherlands (multicentric)	86 (43%)	Males with acute prostatitis included	Randomized stratification for gender	RR 0.95 (0.88 to 1.03)	RR 0.88 (0.78 to 1.00)	NR

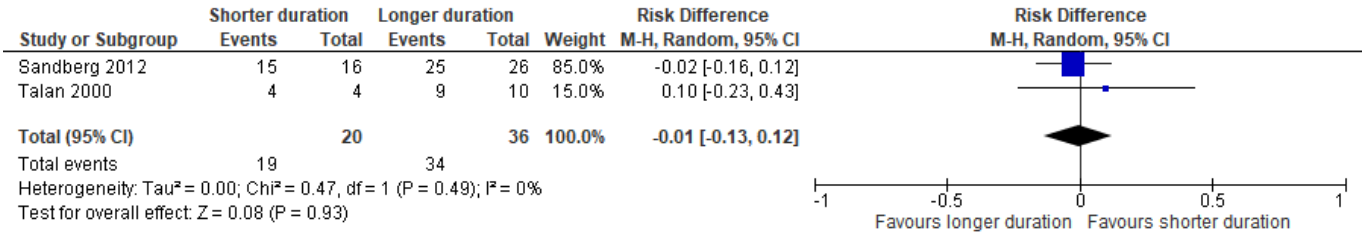
Interpretation: These studies suggest that the minimum effective duration of therapy in male UTI is driven by the presence or absence of acute prostatitis. As the proportion of men with potential prostatitis increases from top to bottom of this table, the effective duration of antibiotic therapy shifts from shorter course to longer course.

NR=not reported; NA=not applicable
*Personal communication with authors: 27 out of 91 men had pain on rectal examination.
Color key:
Green means: men with known prostatitis were specifically excluded, although it was unclear if all male participants were tested for prostatitis
Yellow means: whether or not the male participants had prostatitis was not reported
Orange means: men with prostatitis were included, but male participants were not systematically tested for prostatitis

D) Stratification for complicated UTI with associated gram-negative bacteremia

Subgroup analysis: complicated UTI with associated gram-negative bacteremia

Supplementary Figure 7: Forest plots for Clinical cure (at Test-of-Cure (TOC)) (including Sandberg 2012, Talan 2000, and van Nieuwkoop 2017)



*van Nieuwkoop 2017: Clinical cure rate (10 to 18 days post-treatment) in patients with bacteremia: risk difference (RD) was approximatively -10% with 90% CI (-21% to 2%), thus 7-day was not non-inferior to 14-days in bacteremia (Total number of bacteremic patients was 35, but no stratified data was reported in order to add it to the pooled analysis).

Supporting evidence: cUTI with associated gram-negative bacteremia

Supplementary Table 7: GRADE Evidence Profile

Question: In patients presenting with complicated UTI with associated gram-negative bacteremia, should total duration of antibiotics be **shorter (<=7 days)** rather than **prolonged to >7 days**?

P: In patients presenting with cUTI with associated gram-negative bacteremia
I: shorter total duration of antibiotics (<=7 days)
C: prolonged total duration of antibiotics (>7 days)
Setting: Inpatient and Outpatient

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Shorter duration of Abx (≤7 days)	Prolonged duration of Abx (> 7 days)	Relative (95% CI)	Absolute (95% CI)		
Relapse of bacteremia (at 30 days)												
3 [1-3]	RCTs	serious[a]	not serious	not serious	serious[b]	none	13/391 (3.3%)	9/367 (2.5%)	**RR 1.31** (0.57 to 3.02)	**8 more per 1,000** (from 11 fewer to 50 more)	⊕⊕◯◯ Low	CRITICAL
Mortality (at 30 days)												
3 [1-3]	RCTs	serious[a]	not serious	not serious	serious[c]	none	14/390 (3.6%)	14/367 (3.8%)	**RR 0.93** (0.30 to 2.91)	**3 fewer per 1,000** (from 27 fewer to 73 more)	⊕⊕◯◯ Low	IMPORTANT
Mortality (at 90 days)												
3 [1-3]	RCTs	serious[a]	serious[d]	not serious	serious[e]	none	36/390 (9.2%)	36/367 (9.8%)	**RR 0.94** (0.37 to 2.37)	**6 fewer per 1,000** (from 62 fewer to 134 more)	⊕◯◯◯ Very Low	IMPORTANT
Readmission (at 30 days)												
3 [1-3]	RCTs	very serious[a,g]	not serious	not serious	serious[f]	none	63/391 (16.1%)	70/369 (19.0%)	**RR 0.80** (0.59 to 1.08)	**38 fewer per 1,000** (from 78 fewer to 15 more)	⊕◯◯◯ Very Low	IMPORTANT

Notes:
Clinical failure (i.e. composite outcome of the included main outcomes reported here) was not included in this EP table due to redundancy and lack of granularity.

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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Shorter duration of Abx (≤7 days)	Prolonged duration of Abx (> 7 days)	Relative (95% CI)	Absolute (95% CI)		

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. All included data consists of post-hoc analyses of 3 different RCTs, thus considered at high risk of bias due to potential failure of randomization and serious attrition bias (between 55% and 68% of the patients had a cUTI as the primary source of bacteremia). Outcome measurement time frames varied between studies, with some studies measuring outcomes at an early specific time point after randomization rather than after end of treatment which may bias the assessment in favor of longer duration regimen. These studies were not rated down for risk of bias since this potential bias in favor of the longer course does not lower our confidence in the estimate that shorter is non-inferior to longer).
b. Based on an inferiority margin of 10% (judged clinically significant by the panelists), not rated down for imprecision. Very few events were reported in both groups. Optimal information size criteria not met, and the wide 95% CI suggests fragility of the estimate.
c. Very few events were reported in both groups. Optimal information size criteria not met and wide 95%CI. 95% CI may not include a meaningful difference (i.e. crossing the null value), thus the shorter course failed to show or exclude a beneficial effect as compared to longer course.
d. von Dach 2020 seems to be the main source of heterogeneity. After removing this study from the analysis, the I-square decreases from 59% to 29%.
e. Optimal information size criteria not met and wide 95% CI (which might have been partially influenced by the observed inconsistency). 95% CI may not include a meaningful difference (i.e. crossing the null value), thus the shorter course failed to show or exclude a beneficial effect as compared to longer course.
f. 95% CI may not include a meaningful difference (i.e. crossing the null value), thus the shorter course failed to show or exclude a beneficial effect as compared to longer course
g. Unblinded studies most likely did not affect most outcomes for their assessment or for decision-making that could influence them (except for readmission).

References

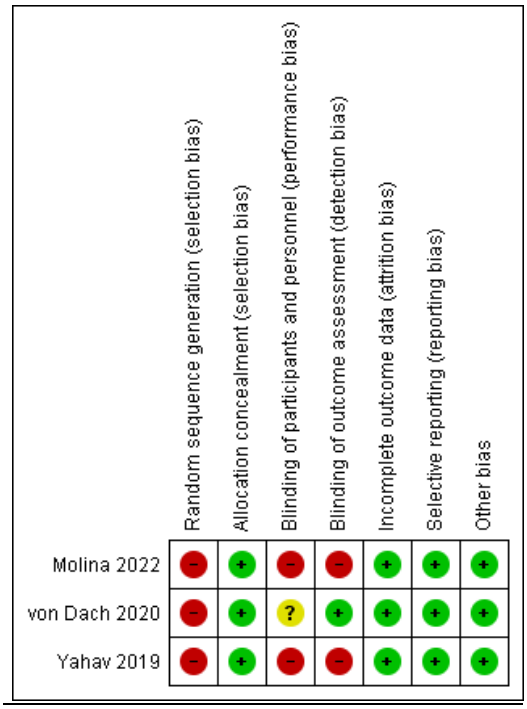
1. Yavah and al. Seven Versus 14 Days of Antibiotic Therapy for Uncomplicated Gram-negative Bacteremia: A Noninferiority Randomized Controlled Trial. Clinical Infectious Diseases® 2019;69(7):1091–8
2. von Dach and al. Effect of C-Reactive Protein–Guided Antibiotic Treatment Duration, 7-Day Treatment, or 14-Day Treatment on 30-Day Clinical Failure Rate in Patients With Uncomplicated Gram-Negative Bacteremia A Randomized Clinical Trial. *JAMA*. 2020;323(21):2160-2169.
3. Molina and al. Seven-versus 14-day course of antibiotics for the treatment of bloodstream infections by Enterobacterales: a randomized, controlled trial. Clin Microbiol Infect 2022;28:550.

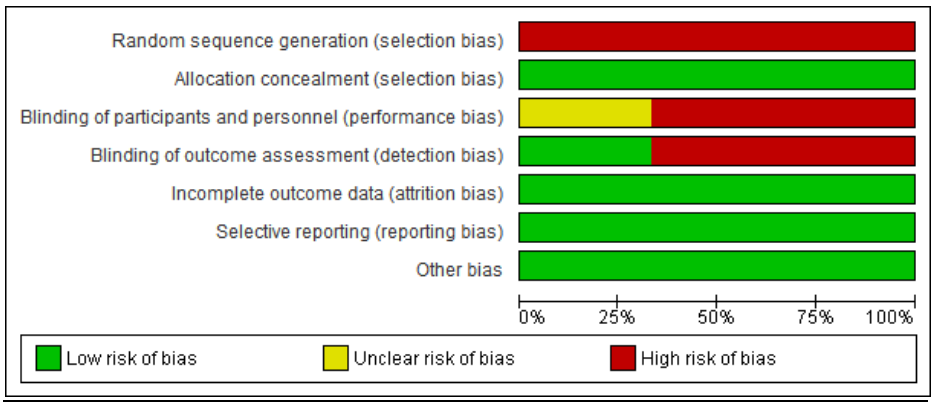
Supplementary Table 8: Characteristics of the included studies on complicated UTI with associated gram-negative bacteremia (n=3, up to 2022)

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 pathogens** (*% of resistance, % of IEAT)*	**Randomisation** *(timing, and criteria for clinical response if reported)*	**Intervention** *(total duration, IV and oral antibiotics)*	**Comparator** *(total duration, IV and oral antibiotics)*
Molina 2022 SHORTEN trial Multicentric (Spain)	Hospitalized and outpatients with Enterobacterales bacteremia, of which 55% had cUTI 2014-2016 N of cUTI:136 In the whole cohort, F: 47% Age: 65 to 68 yo	Non-inferiority trial Margin of 10% for composite outcome of clinical cure, relapse of bacteremia and relapse of fever 28 days after treatment cessation No stratified randomisation for source of infection (post hoc analysis for cUTI)	*E.coli*: 63% ESBL/AmpC : 17% IEAT: 22%	72h after the identification of the Enterobacterales in blood samples (3-4 days after collection) and if controlled of focus of infection and no complicated infections requiring prolonged antibiotics (including prostatitis)	7 days	14 days
Von Dach 2020 Multicentric (Switzerland)	Hospitalized with uncomplicated Gram-negative bacteremia, of which 67% had cUTI 2017-2019 N of cUTI: 224 In the whole cohort, F: 60% Age: 78 to 80yo	Non-inferiority trial Margin of 10% for composite outcome of mortality, recurrent bacteriemia, local suppurative complication, distant complication or restarting antibiotics for clinical worsening attributed to initial organisms at 30 days No stratified randomisation for source of infection (post hoc analysis for cUTI)	*E.coli*: 74% ESBL: 7% IEAT: NR but the impact of delay in AEAT on clinical failure was assessed	On day 5 (±1 d) of microbiologically efficacious antibiotic therapy (if no fever, no hemodynamic instability in the 24 hours of recruitment, and no complicated infections such as abscesses)	7 days	14 days
					Inpatient physicians followed local guidelines for antibiotic choice and administration route; a switch from intravenous to oral administration was allowed per routine practice.	
Yahav 2019 Multicentric (Isarel and Italy)	Hospitalized with aerobic Gram-negative bacteremia, of which 68% had cUTI 2013-2017 N of cUTI: 411 In the whole cohort, F: 53% Age: 71 yo	Non-inferiority trial Margin of 10% for composite outcome of mortality, clinical failure and readmission at 90 days No stratified randomisation for source of infection (post hoc analysis for cUTI)	*Ecoli*: 63% MDR: 18% IEAT: 17%	Patient achieving clinical stability (if hemodynamically stable and afebrile for at least 48 hours, controlled focus of infection) and planned for discharge before day 7	Decisions on the antibiotic agent and oral step-down were decided by the physician in charge without restrictions.	14 days
					The type of empirical or directed antibiotic treatment and the decision on timing of switch to oral antibiotic therapy was also left to the discretion of the treating physician.	
UTI=Urinary Tract Infection; cUTI=complicated UTI; N=number; F=female, y=years; NR=not reported.						

IEAT: inappropriate empiric antibiotic therapy; AEAT: appropriate empiric antibiotic therapy; MDR: multidrug resistant; ESBL= Extended spectrum Beta-Lactamase; AmpC= AmpC beta-lactamase; IV= parenteral.

Supplementary Figure 8: Summary of the Risk of Bias of included studies (Cochrane Risk of bias Tool) (n=3)



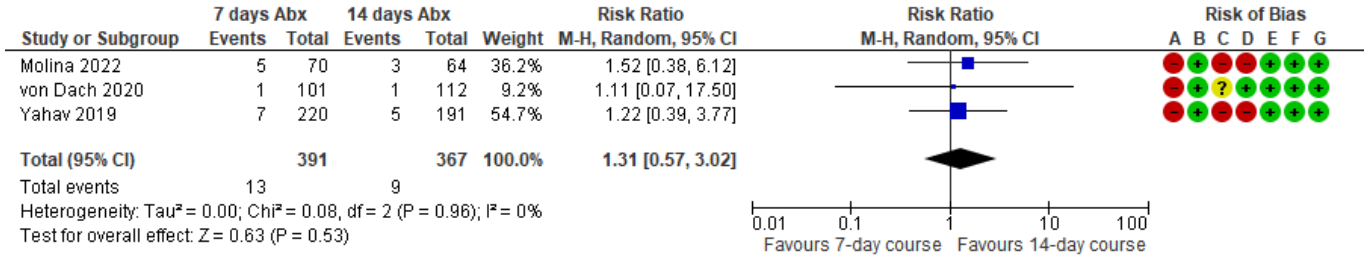


Supplementary Table 9: Assessment of the Risk of Bias of included studies (Cochrane Risk of bias Tool) (n=3)

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)
Molina 2022 SHORTEN trial Multicentric (Spain)	High RoB -Randomization (not further detailed) -Post-hoc analysis for source of infection. No baseline comparison of patients' characteristics reported for this subpopulation.	Low RoB -Centralised automatic system integrated in the electronic case report form	High RoB -Open-label (especially applicable to subjective outcomes)	High RoB -Open-label (especially applicable to subjective outcomes) -Analyst-blinded	Low RoB -All outcomes analysed in the ITT population -No significant lost to follow up	Low RoB	Low RoB -Not industry-funded
Von Dach 2020 Multicentric (Switzerland)	High RoB -Computer-generated randomization with stratification by site -Post-hoc analysis for source of infection. No baseline comparison of patients' characteristics reported for this subpopulation.	Low RoB -Concealment using sealed opaque envelopes	UnclearRoB -Blinding performed from randomization to antibiotic discontinuation -Open-label after antibiotic discontinuation (especially applicable to subjective outcomes)	Low RoB -Blinding performed throughout for outcomes assessors and data analysts	Low RoB -All outcomes analysed in the ITT population -No significant lost to follow up	Low RoB	Low RoB -Not industry-funded -The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review and approval of the manuscript; and decision to submit the manuscript for publication
Yahav 2019 Multicentric (Isarel and Italy)	High RoB -Computer-generated randomization -Post-hoc analysis for source of infection. No baseline comparison of patients' characteristics reported for this subpopulation.	Low RoB -Concealment using sealed opaque envelopes	High RoB -Open-label (especially applicable to subjective outcomes)	High RoB -Open-label (especially applicable to subjective outcomes)	LowRoB -All outcomes analysed in the ITT population -No significant lost to follow up	Low RoB	Low RoB -Not industry-funded
RoB=Risk of Bias; ITT=intention-to-treat.							

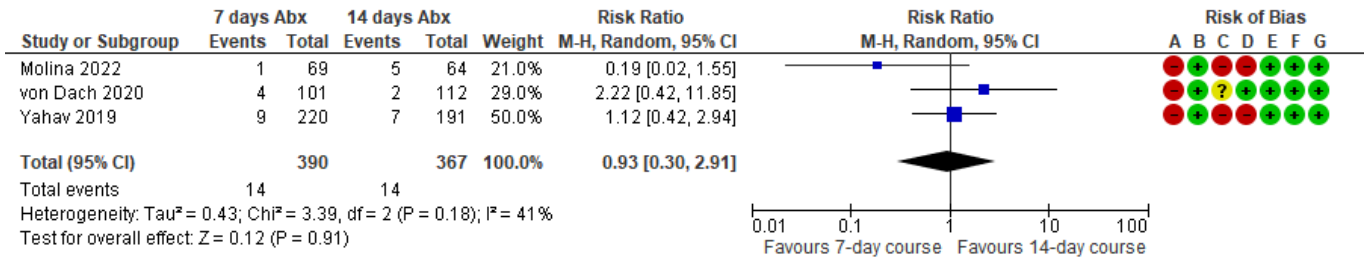
Supplementary Figures 9: Forest plots for each patient-important outcome

9a) Relapse of bacteremia (at 30 days)



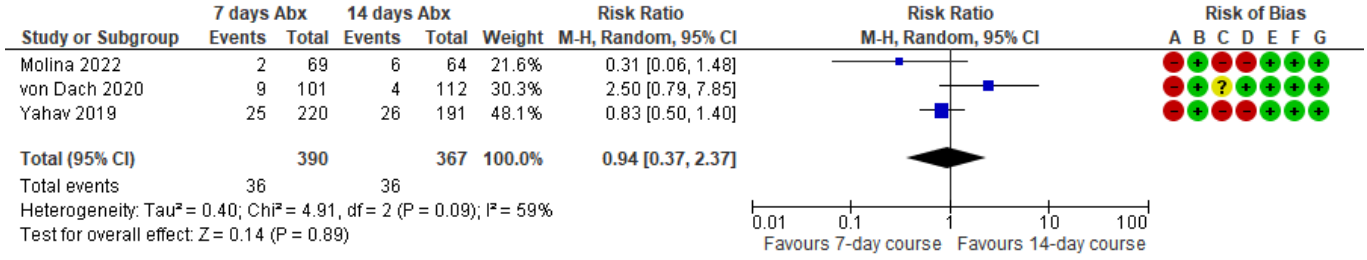
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

9b) Mortality (at 30 days)



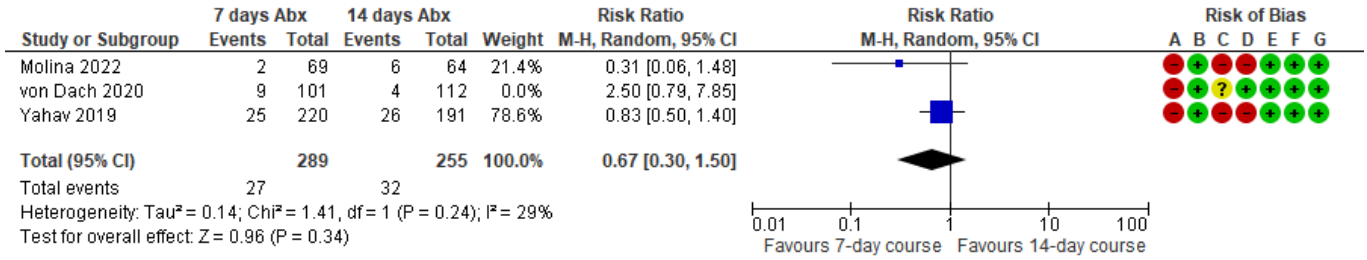
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

9c) Mortality (at 90 days)



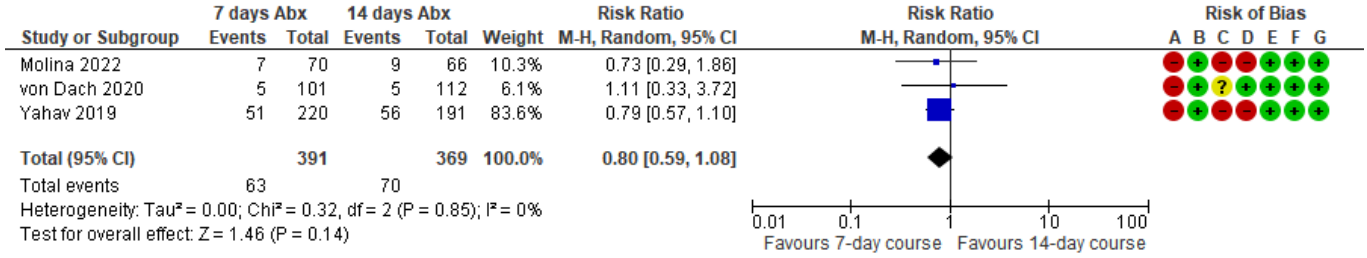
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

9d) Mortality (at 90 days): *Sensitivity analysis after removing von Dach 2020*



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

9e) Readmission (at 30 days)



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

Supplementary Table 10: GRADE Evidence to Decision framework for cUTI with associated gram-negative bacteremia

Summary of Judgments							
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	No included studies
ACCEPTABILITY / STEWARDSHIP	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	**Increased**	Varies	Don't know

Type of Recommendation				
Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	○	○