

Shorter Versus Longer Courses of Antibiotics for Infection in Hospitalized Patients: A Systematic Review and Meta-Analysis

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BACKGROUND: Infection is a leading cause of hospitalization with high morbidity and mortality, but there are limited data to guide the duration of antibiotic therapy.

PURPOSE: Systematic review to compare outcomes of shorter versus longer antibiotic courses among hospitalized adults and adolescents.

DATA SOURCES: MEDLINE and Embase databases, 1990-2017.

STUDY SELECTION: Inclusion criteria were human randomized controlled trials (RCTs) in English comparing a prespecified short course of antibiotics to a longer course for treatment of infection in hospitalized adults and adolescents aged 12 years and older.

DATA EXTRACTION: Two authors independently extracted study characteristics, methods of statistical analysis, outcomes, and risk of bias.

DATA SYNTHESIS: Of 5187 unique citations identified, 19 RCTs comprising 2867 patients met our inclusion

criteria, including the following: 9 noninferiority trials, 1 superiority design trial, and 9 pilot studies. Across 13 studies evaluating 1727 patients, no significant difference in clinical efficacy was observed ($d = 1.6\%$ [95% confidence interval (CI), -1.0% - 4.2%]). No significant difference was detected in microbiologic cure (8 studies, $d = 1.2\%$ [95% CI, -4.1% - 6.4%]), short-term mortality (8 studies, $d = 0.3\%$ [95% CI, -1.2% - 1.8%]), longer-term mortality (3 studies, $d = -0.4\%$ [95% CI, -6.3% - 5.5%]), or recurrence (10 studies, $d = 2.1\%$ [95% CI, -1.2% - 5.3%]). Heterogeneity across studies was not significant for any of the primary outcomes.

CONCLUSIONS: Based on the available literature, shorter courses of antibiotics can be safely utilized in hospitalized patients with common infections, including pneumonia, urinary tract infection, and intra-abdominal infection, to achieve clinical and microbiologic resolution without adverse effects on mortality or recurrence. *Journal of Hospital Medicine* 2018;13:336-342. Published online first January 25, 2018. © 2018 Society of Hospital Medicine

Acute infections are a leading cause of hospitalization and are associated with high cost, morbidity, and mortality.¹ There is a growing body of literature to support shorter antibiotic courses to treat several different infection types.²⁻⁶ This is because longer treatment courses promote the emergence of multidrug resistant (MDR) organisms,⁷⁻⁹ microbiome perturbation,¹⁰ and *Clostridium difficile* infection (CDI).¹¹ They are also associated with more drug side effects, longer hospitalizations, and increased costs.

Despite increasing support for shorter treatment courses, inpatient prescribing practice varies widely, and redundant antibiotic therapy is common.¹²⁻¹⁴ Furthermore, aside from venti-

lator-associated pneumonia (VAP),^{15,16} prior systematic reviews of antibiotic duration have typically included outpatient and pediatric patients,^{3-6,17-19} for whom the risk of treatment failure may be lower.

Given the potential for harm with inappropriate antibiotic treatment duration and the variation in current clinical practice, we sought to systematically review clinical trials comparing shorter versus longer antibiotic courses in adolescents and adults hospitalized for acute infection. We focused on common sites of infection in hospitalized patients, including pulmonary, bloodstream, soft tissue, intra-abdominal, and urinary.^{20,21} We hypothesized that shorter courses would be sufficient to cure infection and associated with lower costs and fewer complications. Because we hypothesized that shorter durations would be sufficient regardless of clinical course, we focused on studies in which the short course of antibiotics was specified at study onset, not determined by clinical improvement or biomarkers. We analyzed all infection types together because current sepsis treatment guidelines place little emphasis on infection site.²² In contrast to prior reviews, we focused exclusively on adult and adolescent inpatients because the risks of a too-short treatment duration may be lower in pediatric and outpatient populations.

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METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.²³ The review was registered on the Prospero database.²⁴

Information Sources and Search Strategy

We performed serial literature searches for articles in English comparing shorter versus longer antibiotics courses in hospitalized patients. We searched MEDLINE via PubMed and Embase (January 1, 1990, to July 1, 2017). We used Boolean operators, Boolean logic, and controlled vocabulary (eg, Medical Subject Heading [MeSH] terms) for each key word. We identified published randomized controlled trials (RCTs) of conditions of interest (MeSH terms: "bacteremia," "sepsis," "pneumonia," "pyelonephritis," "intra-abdominal infection," "cellulitis," "soft tissue infection") that compared differing lengths of antibiotic treatment (keywords: "time factors," "duration," "long course," "short course") and evaluated outcomes (key words: "mortality," "recurrence," "secondary infections"). We hand searched references of included citations. The full search strategy is presented in supplementary Appendix 1.

Study Eligibility and Selection Criteria

To meet criteria for inclusion, a study had to (1) be an RCT; (2) involve an adult or adolescent population age ≥ 12 years (or report outcomes separately for such patients); (3) involve an inpatient population (or report outcomes separately for inpatients); (4) stipulate a short course of antibiotics per protocol prior to randomization and not determined by clinical response, change in biomarkers, or physician discretion; (5) compare the short course to a longer course of antibiotics, which could be determined either per protocol or by some other measure; and (6) involve antibiotics given to treat infection, not as prophylaxis.

Two authors (SR and HCP) independently reviewed the title and/or abstracts of all articles identified by the search strategy. We calculated interrater agreement with a kappa coefficient. Both authors (SR and HCP) independently reviewed the full text of each article selected for possible inclusion by either author. Disagreement regarding eligibility was adjudicated by discussion.

Data Abstraction

Two authors (SR and HCP) independently abstracted study methodology, definitions, and outcomes for each study using a standardized abstraction tool (see supplementary Appendix 2).

Study Quality

We assessed article quality using the Cochrane Collaboration's tool,²⁵ which evaluates 6 domains of possible bias, including sequence generation, concealment, blinding, and incomplete or selective outcome reporting. The tool is a 6-point scale, with 6 being the best score. It is recommended for assessing bias because it evaluates randomization and allocation concealment, which are not included in other tools.²⁶ We did not exclude studies based on quality but considered studies with scores of 5-6 to have a low overall risk of bias.

Study Outcomes and Statistical Analysis

Our primary outcomes were clinical cure, microbiologic cure, mortality, and infection recurrence. Secondary outcomes were secondary MDR infection, cost, and length of stay (LOS). We conducted all analyses with Stata MP version 14 (StataCorp, College Station, TX). For each outcome, we reported the difference (95% confidence interval [CI]) between treatment arms as the rate in the short course arm minus the rate in the long course arm, consistent with the typical presentation of noninferiority data. When not reported in a study, we calculated risk difference and 95% CI using reported patient-level data. Positive values for risk difference favor the short course arm for favorable outcomes (ie, clinical and microbiologic cure) and the long course arm for adverse outcomes (ie, mortality and recurrence). A meta-analysis was used to pool risk differences across all studies for primary outcomes and for clinical cure in the community-acquired pneumonia (CAP) subgroup. We also present results as odds ratios and risk ratios in the online supplement. All meta-analyses used random effects models, as described by DerSimonian and Laird,^{27,28} with variance estimates of heterogeneity taken from the Mantel-Haenszel fixed effects model. We investigated heterogeneity between studies using the χ^2 I² statistic. We considered a $P < .1$ to indicate statistically significant heterogeneity and classified heterogeneity as low, moderate, or high on the basis of an I² of 25%, 50%, or 75%, respectively. We used funnel plots to assess for publication bias.

RESULTS

Search Results

We identified 5187 unique citations, of which 110 underwent full-text review (Figure 1). Reviewer agreement for selection of title and/or abstracts for full evaluation was 99.1% (kappa = 0.71). Nineteen RCTs with a total of 2867 patients met inclusion criteria and were included in the analysis.²⁹⁻⁴⁷

Characteristics of Included Studies

Publication years ranged from 1991 to 2015 (Table). Study populations were primarily from Europe (n = 9) or the United States (n = 5). Pneumonia was the most common infection studied, with 3 studies evaluating VAP and 9 studies evaluating CAP. There were also 3 studies of intra-abdominal infections, 2 studies of urinary tract infections (UTIs), 1 study of typhoid fever, and 1 study of hospital-acquired infection of unknown origin. No studies of bacteremia or soft tissue infections met inclusion criteria. Short courses of antibiotics ranged from 1 to 8 days, while long courses ranged from 3 to 15 days.

Common study outcomes included clinical cure or efficacy (composite of symptom cure and improvement; n = 13), infection recurrence (n = 10), mortality (n = 9), microbiologic cure (n = 8), and LOS (n = 7; supplementary Table 1).

Nine studies were pilot studies, 1 was a traditional superiority design study, and 9 were noninferiority studies with a prespecified limit of equivalence of either 10% (n = 7) or 15% (n = 2).

TABLE. Characteristics of Included Studies

Author	Year	Country	Number of Patients ^a	Patient Location	Infection Type	Short Course Antibiotic	Short Course Duration (days)	Long Course Antibiotic	Long Course Duration (days)	Primary Outcome	Study Design
Bohte et al. ²⁹	1995	Netherlands	104	Ward	CAP	Azithromycin	5	Erythromycin or benzylpenicillin	10 or 5 days past last fever	Clinical cure by day 21	Superiority
Capellier et al. ³⁰	2012	France	225	ICU	VAP	Beta-lactam, aminoglycoside	8	Beta-lactam, aminoglycoside	15	Clinical cure at day 21	Non-inferiority
Chastre et al. ³¹	2003	France	401	ICU	VAP	Beta-lactam, aminoglycoside or fluoroquinolone	8	Beta-lactam, aminoglycoside or fluoroquinolone	15	All-cause mortality at day 28, documented recurrence, antibiotic free days	Non-inferiority
Chaudhry et al. ³²	2000	Pakistan	50	Ward	SBP	Cefoperazone	5	Cefoperazone	10	Infection-related and hospitalization mortality ^b	Pilot
Darouiche et al. ³³	2014	USA	55	Ward	CA-UTI	Physician discretion ^c	5	Physician discretion ^c	10	Clinical cure at end of therapy (day 5 or 10)	Non-inferiority
deGier et al. ³⁴	1995	Netherlands	34	Ward	c-UTI	Fleroxacin	7	Fleroxacin	14	Microbiologic cure 4 to 6 weeks post therapy ^b	Pilot
Dunbar et al. ³⁵	2003	USA	162	Ward, outpatient	CAP	Levofloxacin	5	Levofloxacin	10	Clinical success at posttherapy (7-14 days after last antibiotics)	Non-inferiority
Gasem et al. ³⁶	2003	Indonesia	55	Ward	Enteric fever	Ciprofloxacin	7	Chloramphenicol	14	Clinical cure at day 7	Pilot
Kollef et al. ³⁷	2012	International	167	ICU	VAP	Doripenem	7	Imipenem-cilastatin	10	Clinical cure at end of therapy (day 10)	Non-inferiority
Kuzman et al. ³⁸	2005	International	171	Ward	CAP	Azithromycin	4-7	Cefuroxime	8-11	Clinical efficacy at posttreatment (day 10-14)	Pilot
Leophonte et al. ³⁹	2002	France	244	Ward	CAP	Ceftriaxone	5	Ceftriaxone	10	Apyrexia and no further antibiotics at day 10	Non-inferiority
Rizzato et al. ⁴⁰	1995	Italy	40	Ward	CAP	Azithromycin	3	Clarithromycin	8+	Clinical cure at day 10 ^b	Pilot
Runyon et al. ⁴¹	1991	USA	90	Ward	SBP	Cefotaxime	5	Cefotaxime	10	Hospitalization and all-cause mortality ^b	Non-inferiority
Sawyer et al. ⁴²	2015	USA-Canada	517	Ward	Complicated intra-abdominal infection	Physician discretion ^d	4	Physician discretion ^d	2 days after resolution of SIRS, maximum 10 days	Composite mortality, surgical-site infection, recurrent intra-abdominal infection	Non-inferiority
Scawn et al. ⁴³	2012	UK	46	ICU	Hospital-acquired infection of unknown origin	Meropenem, teicoplanin	2	Meropenem, teicoplanin	7	Composite mortality and need for further antibiotics	Pilot
Schonwald et al. ⁴⁴	1994	Croatia	142	Ward	CAP	Azithromycin	3	Roxithromycin	10	Clinical cure at day 14	Pilot
Schonwald et al. ⁴⁵	1999	Croatia	98	Ward	CAP	Azithromycin	1	Azithromycin	3	Clinical cure at day 10 to 14	Pilot
Siegel et al. ⁴⁶	1999	USA	46	Ward	CAP	Cefuroxime	7	Cefuroxime	10	Clinical cure at day 10 to 14	Pilot
Zhao et al. ⁴⁷	2014	China	220	Ward	CAP	Levofloxacin	5	Levofloxacin	7+	Overall efficacy at 7 to 14 days post therapy	Non-inferiority

^a Number of patients included in primary outcome and/or subset of patients hospitalized.

^b Primary outcome(s) not specified; outcome(s) discussed first and/or most extensively considered to be primary outcome(s).

^c Standard choices oral fluoroquinolone and amoxicillin; aztreonam and vancomycin used in patients unable to tolerate oral antibiotics; antibiotic choice based on prior sensitivities if available.

^d Acceptable if consistent with Surgical Infection Society and Infectious Diseases Society of America guidelines.

NOTE: Abbreviations: CAP, community-acquired pneumonia; CA-UTI, catheter-associated urinary tract infection; c-UTI, complicated urinary tract infection; ICU, intensive care unit; SBP, spontaneous bacterial peritonitis; SIRS, systemic inflammatory response syndrome; UK, United Kingdom; USA, United States of America; VAP, ventilator-associated pneumonia.

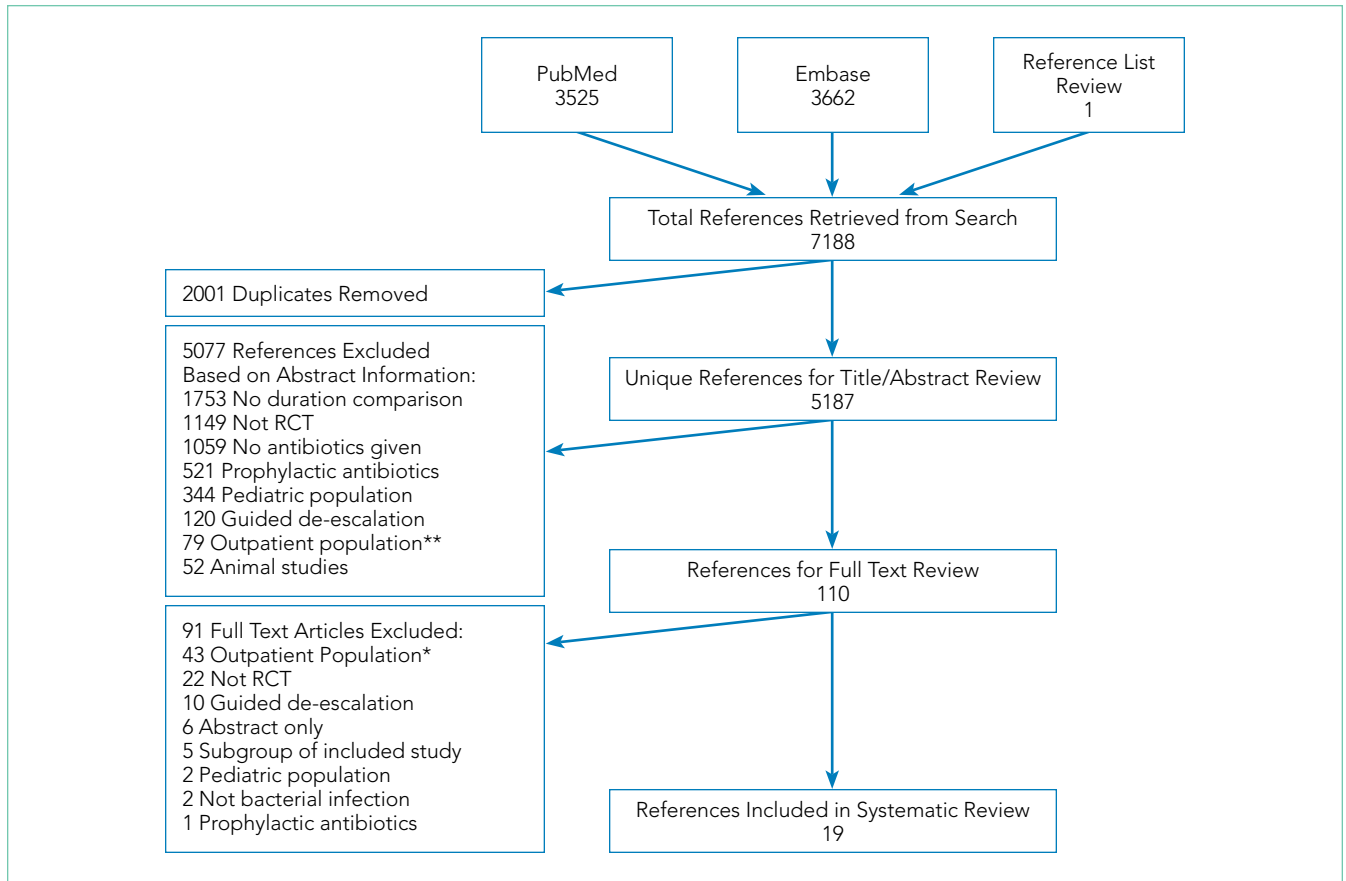


FIG 1. Flow diagram for literature review and study selection. NOTE: **All 79 of these articles included an outpatient-only population. *Twenty-six of these 43 articles were excluded after full-text review because the population contained both inpatients and outpatients but did not provide separate outcomes for the inpatient subgroup. Seventeen articles contained an outpatient-only population. Abbreviation: RCT, randomized controlled trial.

Clinical Cure and Efficacy

Thirteen studies of 1727 patients evaluated clinical cure and efficacy (Figure 2).^{29,30,33,35-40,44-47} The overall risk difference was $d = 1.6\%$ (95% CI, -1.0% - 4.2%), and the pooled odds ratio was 1.11 (95% CI, 0.85-1.45; supplementary Table 2). There was no heterogeneity between studies ($I^2 = 0\%$, $P = .55$). Five of 6 studies with a noninferiority design met their prespecified margin, while 1 study of VAP failed to meet the 15% noninferiority margin ($d = -11.2\%$ [95% CI, -26.3% - 3.8%]).³⁷

Nine studies of 1225 patients evaluated clinical cure and efficacy in CAP (supplementary Figure 1).^{29,35,38-40,44-47} The overall risk difference was $d = 2.4\%$ (95% CI, -0.7% - 5.5%). There was no heterogeneity between studies ($I^2 = 0\%$, $P = .45$).

Microbiologic Cure

Eight studies of 366 patients evaluated microbiologic cure (supplementary Figure 2).^{32-34,36,38,40,41,47} The overall risk difference was $d = 1.2\%$ (95% CI, -4.1% - 6.4%). There was no statistically significant heterogeneity between studies ($I^2 = 13.3\%$, $P = .33$).

Mortality

Eight studies of 1740 patients evaluated short-term mortality (in hospital to 45 days; Figure 2),^{30-32,37,39,41,43} while 3 studies of

654 patients evaluated longer-term mortality (60 to 180 days; supplementary Figure 3).^{30,31,33} The overall risk difference was $d = 0.3\%$ (95% CI, -1.2% - 1.8%) for short-term mortality and $d = -0.4\%$ (95% CI, -6.3% - 5.5%) for longer-term mortality. There was no heterogeneity between studies for either short-term ($I^2 = 0.0\%$, $P = .66$) or longer-term mortality ($I^2 = 0.0\%$, $P = .69$).

Infection Recurrence

Ten studies of 1554 patients evaluated infection recurrence (Figure 2).^{30-34,40-42,45,46} The overall risk difference was $d = 2.1\%$ (95% CI, -1.2% - 5.3%). There was no statistically significant heterogeneity between studies ($I^2 = 21.0\%$, $P = .25$). Two of the 3 studies with noninferiority design (both evaluating intra-abdominal infections) met their prespecified margins.^{41,42} In Chastre et al.,³¹ the overall population ($d = 3.0\%$; 95% CI, -5.8% - 11.7%) and the subgroup with VAP due to nonfermenting gram-negative bacilli (NF-GNB; $d = 15.2\%$; 95% CI, -0.9% - 31.4%) failed to meet the 10% noninferiority margin.

Secondary Outcomes

Three studies^{30,31,42} of 286 patients (with VAP or intra-abdominal infection) evaluated the emergence of MDR organisms. The overall risk difference was $d = -9.0\%$ (95% CI, -19.1% - 1.1% ; $P = .081$). There was no statistically significant

heterogeneity between studies ($I^2 = 7.6\%$, $P = .34$).

Seven studies examined LOS—3 in the intensive care unit (ICU)^{30,31,43} and 4 on the wards^{32,36,40,41}—none of which found significant differences between treatment arms. Across 3 studies of 672 patients, the weighted average for ICU LOS was 23.6 days in the short arm versus 22.2 days in the long arm. Across 4 studies of 235 patients, the weighted average for hospital LOS was 23.3 days in the short arm versus 29.7 days in the long arm. This difference was driven by a 1991 study⁴¹ of spontaneous bacterial peritonitis (SBP), in which the average LOS was 37 days and 50 days in the short- and long-course arms, respectively.

Three studies^{32,41,43} of 186 total patients (with SBP or hospital-acquired infection of unknown origin) examined the cost of antibiotics. The weighted average cost savings for shorter courses in 2016 US dollars⁴⁸ was \$265.19.

Three studies^{30,33,43} of 618 patients evaluated cases of CDI, during 10-, 30-, and 180-day total follow-up. The overall risk difference was $d = 0.7\%$ (95% CI, -1.3% - 2.8%), with no statistically significant heterogeneity between studies ($I^2 = 0\%$, $P = .97$).

Study Quality

Included studies scored 2-5 on the Cochrane Collaboration Risk of Bias Tool (supplementary Figure 4). Four studies had an overall low risk of bias,^{36,37,43,46} while 15 had a moderate to high risk of bias (supplementary Table 3).^{29-35,38-42,44,45,47} Common sources of bias included inadequate details to confirm adequate randomization and/or concealment ($n = 13$) and lack of adequate blinding ($n = 18$). Two studies were stopped early,^{37,42} and 3 others were possibly stopped early because it was unclear how the number of participants was determined.^{29,33,47} Covariate imbalance (failure of randomization) was present in 2 studies.^{37,47} There was no evidence of selective outcome reporting or publication bias based on the funnel plots (supplementary Figure 5).

DISCUSSION

In this study, we performed a systematic review and meta-analysis of RCTs of shorter versus longer antibiotic courses for adults and adolescents hospitalized for infection. The rate of clinical cure was indistinguishable between patients randomized to shorter versus longer durations of antibiotic therapy, and the meta-analysis was well powered to confirm noninferiority. The lower 95% CI indicates that any potential benefit of longer antibiotics is not more than 1%, far below the typical margin of noninferiority. Subgroup analysis of patients hospitalized with CAP also showed noninferiority of a prespecified shorter treatment duration.

The rate of microbiologic cure was likewise indistinguishable, and the meta-analysis was again well powered to confirm noninferiority. Any potential benefit of longer antibiotics for microbial cure is quite small (not more than 4%).

Our study also demonstrates noninferiority of prespecified shorter antibiotic courses for mortality. Shorter- and longer-term mortality were both indistinguishable in patients randomized to shorter antibiotic courses. The meta-analyses

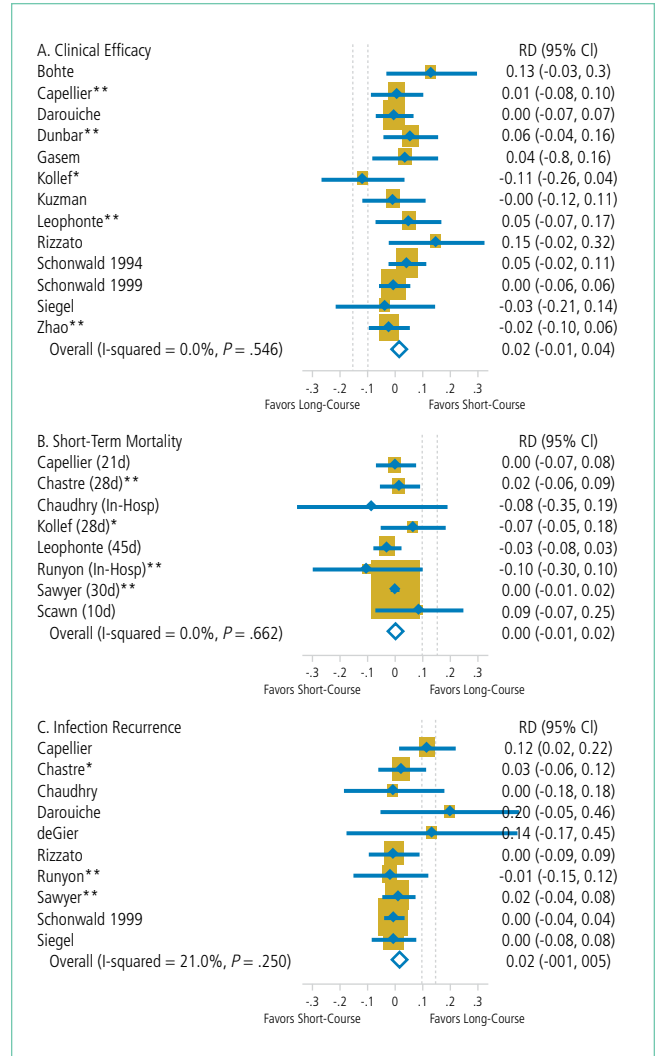


FIG 2. Forest plots (clinical efficacy, short-term mortality, infection recurrence). NOTE: Fifteen percent was used as the limit of equivalence for the difference between short-course and long-course groups in 2 studies (Kollef et al.³⁷ and Runyon et al.⁴¹). Ten percent was used as the limit of equivalence for the difference between short-course and long-course groups in 7 studies (Capellier et al.,³⁰ Chastre et al.,³¹ Darouiche et al.,³³ Dunbar et al.,³⁵ Leophonte et al.,³⁹ Sawyer et al.,⁴² and Zhao et al.⁴⁷). For favorable outcomes (eg, clinical efficacy), positive values favor the short-course arm, and the lower limit of the 95% confidence interval must be $\geq -10\%$ or $\geq -15\%$ to confirm noninferiority. For adverse outcomes (eg, mortality and infection recurrence), negative values favor the short course group, and the upper limit of the 95% confidence interval must be $\leq 10\%$ or $\leq 15\%$ to confirm noninferiority. **Met prespecified noninferiority margin. *Evaluated noninferiority but did not meet prespecified margin.

for mortality were well powered, with any potential benefit of longer antibiotic durations being less than 2% for short-term and less than 6% for long-term mortality.

We also examined for complications related to antibiotic therapy. Infection recurrence was indistinguishable, with any potential benefit of longer antibiotics being less than 6%. Select infections (eg, VAP due to NF-GNB, catheter-associated UTI) may be more susceptible to relapse after shorter treatment courses, while most patients hospitalized with infection do not have an increased risk for relapse with shorter treatment courses. Consistent with other studies,⁸ the emergence of

MDR organisms was 9% less common in patients randomized to shorter antibiotic courses. This difference failed to meet statistical significance, likely due to poor power. The emergence of MDR pathogens was included in just 3 of 19 studies, underscoring the need for additional studies on this outcome.

Although our meta-analyses indicate noninferiority of shorter antibiotic courses in hospitalized patients, the included studies are not without shortcomings. Only 4 of the included studies had low risk of bias, while 15 had at least moderate risk. The nearly universal source of bias was a lack of blinding. Only 1 study³⁷ was completely blinded, and only 3 others had partial blinding. Adequate randomization and concealment were also lacking in several studies. However, there was no evidence of selective outcome reporting or publication bias.

Our findings are consistent with prior studies indicating noninferiority of shorter antibiotic courses in other settings and patient populations. Pediatric studies have demonstrated the success of shorter antibiotic courses in both outpatient⁴⁹ and inpatient populations.⁵⁰ Prior meta-analyses have shown noninferiority of shorter antibiotic courses in adults with VAP^{15,16}; in neonatal, pediatric, and adult patients with bacteremia¹⁷; and in pediatric and adult patients with pneumonia and UTI.^{3-6,18,19} Our meta-analysis extends the evidence for the safety of shorter treatment courses to adults hospitalized with common infections, including pneumonia, UTI, and intra-abdominal infections. Because neonatal, pediatric, and nonhospitalized adult patients may have a lower risk for treatment failure and lower risk for mortality in the event of treatment failure, we focused exclusively on hospitalized adults and adolescents.

In contrast to prior meta-analyses, we included studies of multiple different sites of infection. This allowed us to assess a large number of hospitalized patients and achieve a narrow margin of noninferiority. It is possible that the benefit of optimal treatment duration varies by type of infection. (And indeed, absolute duration of treatment differed across studies.) We used a random-effects framework, which recognizes that the true benefit of shorter versus longer duration may vary across study populations. The heterogeneity between studies in our meta-analysis was quite low, suggesting that the results are not explained by a single infection type.

There are limited data on late effects of longer antibiotic courses. Antibiotic therapy is associated with an increased risk for CDI for 3 months afterwards.¹¹ However, the duration of follow-up in the included studies rarely exceeded 1 month, which could underestimate incidence. The effect of antibiotics on gut microbiota may persist for months, predisposing patients to secondary infections. It is plausible that disruption in gut microbiota and risk for CDI may persist longer in patients treated with longer antibiotic courses. However, the existing studies do not include sufficient follow-up to confirm or refute this hypothesis.

Our review has several limitations. First, we included studies that compared an a priori-defined short course of antibiotics to a longer course and excluded studies that defined a short course of antibiotics based on clinical response. Because we did not specify an exact length for short or long courses, we

cannot make explicit recommendations about the absolute duration of antibiotic therapy. Second, we included multiple infection types. It is possible that the duration of antibiotics required may differ by infection type. However, there were not sufficient data for subgroup analyses for each infection type. This highlights the need for additional data to guide the treatment of severe infections. Third, not all studies considered antibiotic duration in isolation. One study included a catheter change in the short arm only, which could have favored the short course.³³ Three studies used different doses of antibiotics in addition to different durations.^{35,45,47} Fourth, the quality of included studies was variable, with lack of blinding and inadequate randomization present in most studies.

CONCLUSION

Based on the available literature, shorter courses of antibiotics can be safely utilized in hospitalized adults and adolescents to achieve clinical and microbiologic resolution of common infections, including pneumonia, UTI, and intra-abdominal infection, without adverse effect on infection recurrence. Moreover, short- and longer-term mortality are indistinguishable after treatment courses of differing duration. There are limited data on the longer-term risks associated with antibiotic duration, such as secondary infection or the emergence of MDR organisms.

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