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Clin-Star Corner: What's New at the Interface of Geriatrics, Infectious Diseases and Antimicrobial Stewardship

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Abstract

Antibiotics are among the leading causes of adverse drug events in older adults. Short-course antibiotic therapy has been shown to work as well as the traditional longer durations for many types of infections. Antibiotic stewardship programs including deprescribing strategies, have shown reduction in patient readmissions and mortality among older adults. We identified practice changing clinical trials focusing on three major domains of overprescribing antibiotics in older adults - community acquired pneumonia, urinary tract infections, and gram-negative bacteremia. The selected articles underscore the safety and effectiveness of shorter durations of antibiotic treatment for infections in older adults, thus highlighting an opportunity for deprescribing in the aging population. By optimizing antibiotic use, we stand to reduce adverse events and enhance overall health outcomes in older adults.

BACKGROUND

Infections are a common cause of mortality and morbidity in older adults. Immune senescence, comorbidities, and atypical clinical presentations in older adults can lead to both under- and over-diagnosis of infections. Delay in administration of antimicrobials can lead to poor outcomes; however, overuse of antimicrobials can lead to drug adverse events and antimicrobial resistance. Almost 75% of antibiotic prescriptions in long term care settings are either not clinically indicated, or of incorrect duration or dose.[1] Atypical presentations, high colonization rates, and increased risk of decompensation make it tough

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to refrain from starting an antibiotic. Shortening the duration of antibiotic use may be a safer avenue for deprescribing in older adults[2]. Antibiotic overuse has exacerbated during the COVID-19 pandemic.[3] Several practice changing articles focusing on appropriate diagnosis and treatment of infections in older adults have been recently published.[1,4] Short-course antibiotic therapy has been shown to work as well as the traditional longer durations for many types of infections, and is associated with lower incidence of adverse events.[5,6] Reflecting this shift in thinking, the American College of Physicians released new guidelines recommending a short course of antibiotics for urinary tract infections, pneumonia, acute bronchitis with chronic obstructive pulmonary disease, and cellulitis.[7]

Our objective was to identify three recent practice changing clinical trials focusing on infections in older adults. The chosen articles highlight three major domains of overprescribing antibiotics in older adults- community acquired pneumonia (CAP), urinary tract infections (UTI), and gram-negative bacteremia (GNB).

METHODS

We selected articles for a narrative review by conducting a PubMed database search restricted to randomized controlled trials (RCTs) published from June 1, 2020– July 31, 2021, English language, humans, and older adults (65 years). The timing of the search strategy is one year prior to date of invitation from Clin-Star Leadership to perform this review. The search strategy combined terms related to infections, infectious, bacteremia, and pneumonia (supplementary table 1). In addition, we also reviewed clinical trials presented at Infectious Disease Society of America (IDSA) 2021 annual scientific meeting as noteworthy clinical trials.[8] We excluded clinical trials related to infections in transplant patients and patients with human immunodeficiency virus. We initially included clinical trials related to COVID-19.

One author (SDA) identified 22 major articles (supplementary table 2) after reviewing 405 total article titles and abstracts. Three coauthors (SDA, KES, LM) reviewed abstracts and full texts to determine their eligibility. Five articles were selected based on their impact on older adults, quality of methods, and treatment decisions faced by geriatrics physicians. Due to constant updates to the COVID-19 treatment guidelines, we eventually excluded clinical trials related to treatment of COVID-19. We recommend referring to IDSA and Centers for Disease Control and Prevention's Real Time Learning Network website[9] (collaborator of American Geriatrics Society) for updated information on COVID-19 therapeutics, diagnostics, vaccines, infection prevention, complications, and guidelines. After conducting the literature search, it was evident that the most eligible RCTs focused on treatment of three common infections in older adults. We eventually selected three high-impact practice changing articles for detailed discussion. Disagreements between authors were resolved by discussion. We categorized all five articles in Table 1.

SUMMARY OF STUDIES

Discontinuing beta-lactam treatment after 3 days for patients with community-acquired pneumonia in non-critical care wards (PTC): a double-blind, randomised, placebo-controlled, non-inferiority trial.[10]

Study summary—In this non-inferiority randomized controlled trial across 16 centers in France, adults (median age, 73 years) admitted with CAP who were clinically stable after three days of beta-lactam therapy were randomized to either placebo or amoxicillin-clavulanic acid for the remaining five days. Inclusion criteria included being afebrile with stable heart and respiratory rate, a systolic blood pressure 90 mm Hg, and oxygen saturation 90%. Important exclusions included severe CAP (defined as those requiring ICU care), immunocompromised patients, and those with healthcare-associated pneumonia. The primary endpoint was clinical cure at day 15 defined by absence of fever, absence of or improvement in respiratory symptoms (dyspnea, cough, purulent sputum, and crackles), and absence of need for additional antibiotics. Rates of cure were non-inferior in the placebo arm compared to the beta-lactam arm in the per protocol analysis (78% vs 68% respectively, and intention to treat analysis (77% vs 68% respectively). Adverse events were similar between groups.

Strengths and limitations—Some limitations included: lower than projected cure rates, less than half of the screened population meeting eligibility criteria, and lack of antimicrobial coverage for atypical organisms as recommended by the IDSA guidelines.[11] However, enrolled patients had clinical characteristics similar to clinical practice enhancing generalizability.

Interpretation and implications—These data suggest that three days of antibiotics are likely sufficient for CAP among non-immunocompromised, non-severely ill patients that show clinical improvement at day three.

Effect of 7 vs 14 Days of Antibiotic Therapy on Resolution of Symptoms Among Afebrile Men With Urinary Tract Infection: A Randomized Clinical Trial.[12]

Study summary—UTIs in men are often considered 'complicated UTIs' triggering longer course of antibiotic therapy. In a continuing effort to shorten courses of antibiotics for common infections, U.S. Veterans Affairs investigators enrolled 272 afebrile men (median age, 69 years) with one or more symptoms attributable to the urinary tract. Patients were enrolled at the end of their 7-day outpatient regimens if they were being treated with ciprofloxacin or trimethoprim/sulfamethoxazole, and randomized to an additional 7 days of their original antibiotic or to placebo. Exclusion criteria included fever or growth of an organism that was not susceptible to the two antibiotics. In intent-to-treat and per protocol analyseson day 14, symptom resolution was not significantly different in the 14-day and 7-day groups (≈92%). Subgroup analyses of patients with positive (77%) or negative (23%) urine cultures also showed no differences. At 28 days, recurrence of symptoms was similar in both treatment groups (≈12%). No patients progressed to febrile UTI or upper UTI, and incidence of adverse events was similar in both treatment groups.

Strengths and limitations—This clinical trial is the most rigorous to date in evaluating antibiotic duration in male UTI, and lays the foundation for many future UTI trials. Limitations include possible confounding bias from the study design and clinical definition of UTI which could bias results toward the null. Therapy in the trial was limited to ciprofloxacin and trimethoprim/sulfamethoxazole as there was a paucity of data supporting other agents like amoxicillin-clavulanate or nitrofurantoin in male UTI.

Interpretation and implications—The results from this clinical trial support using a 7-day antibiotic course for afebrile men with UTI. These findings also suggest that even shorter antibiotic courses for UTI could be studied in the future. Since this trial ended, a black box warning was included for ciprofloxacin packaging which highlights that the risks for adverse events generally offsets the benefits of use in uncomplicated UTIs.

Effect of C-Reactive Protein (CRP)–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[13]

Study summary—In this randomized controlled clinical trial involving more than 500 adults (median age, 79 years) with uncomplicated gram-negative bacteremia (GNB) conducted in three Swiss tertiary care hospitals, 7-day antibiotic therapy guided by use of CRP was non inferior to 14-day therapy. Adults with uncomplicated GNB were randomized on day five of treatment (if they were afebrile for 24 hours) in a 1:1:1 ratio to an individualized CRP-guided antibiotic treatment duration, fixed 7-day treatment, or fixed 14-day treatment. The primary outcome was the 30-day clinical failure rate, defined as the presence of at least one of the following: recurrent bacteremia, local or distant complication, restarting antibiotic therapy due to clinical worsening, any cause mortality (with a non-inferiority margin of 10%). 30-day clinical failure rates in CRP-guided group (2.4%) and 7-day treatment group (6.6%) were non-inferior to the 14-day treatment group (5.5%).

Strengths and limitations—Limitations include low observed event rate, low adherence, and wide range of treatment durations in the CRP-guided group. Although the CRP-guided group had numerically fewer treatment failures than the 7-day group, the difference was small and of unclear clinical and statistical significance. Overall, this study builds on other clinical trials of short courses for gram negative bacteremia, and suggests a tailored approach to the individual patient by using biomarkers like CRP to reduce antibiotic duration.

Interpretation and implications—This study reinforces the principle that antibiotic duration does not be predefined in the initial period of acute illness; rather, it should be determined over time in line with the patient's ongoing response. The study results are consistent with many prior and recent randomized controlled trials that support 7-day treatment for uncomplicated GNB.[14,15]

CONCLUSION

In this review, we discussed three practice changing clinical trials published in the past year that highlight the safety and effectiveness of shorter durations of antibiotic

treatment for infections in older adults. Together, these studies highlight opportunities to optimize antibiotic use in older adults as well as highlight future research opportunities in deprescribing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Financial Disclosure:

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"Key Points":

- Shorter durations are just as effective as longer courses of antibiotics for common infections in older adults.

- Shortening the duration of antibiotic use is associated with lower incidence of adverse events, and provides another avenue for deprescribing in older adults.

"Why does this paper matter?":

We identified practice changing clinical trials focusing on three major domains of overprescribing antibiotics in older adults - community acquired pneumonia, urinary tract infections, and gram-negative bacteremia. The selected articles emphasize the safety and effectiveness of shorter durations of antibiotic treatment for infections in older adults, thus highlighting an opportunity for deprescribing in the aging population.

Table 1:

Practice changing clinical trials focusing on infections in older adults (6/2020–7/2021)

Source	Study Characteristics	Sample Size (% male)	Median Age (Range)	Infection	Primary Outcome	Key Takeaways
Dinh A et al, 2020[10]	Double-blind, randomized, placebo-controlled, non-inferiority trial in **16 French centers**	303 (60% male)	73 (54–85 years)	Community-acquired pneumonia	Clinical cure at day 15	3 days comparable to 8 days of beta lactam treatment if clinically stable at the time of discontinuing treatment
Drekonja DM et al, 2021[12]	Double-blind, placebo-controlled, randomized trial at **2 US Veterans Affairs medical centers (in MN and TX)**	272 (100% male)	69 (62–73) years	Male urinary tract infection	**Resolution of UTI symptoms by day 14**	7 days comparable to 14 days of ciprofloxacin or trimethoprim in afebrile men with suspected UTI
Molina J et al, 2021[14]	Open-label, multicenter, randomized, controlled, phase IV trial in **5 Spanish hospitals**	248 (53% male)	65 (53–77 years)	Entero-bacterales bacteremia	Clinical cure, relapse of bacteremia and fever	7 days comparable to 14 days of antibiotics when treating Enterobacterales bacteremia with adequate source control
von Dach E et al, 2020[13]	Multicenter, noninferiority, point-of-care randomized controlled trial in **3 Swiss tertiary care hospitals**	504 (39% male	79 (68–86 years)	Gram-negative bacteremia	30-day clinical failure rate	7 days was non-inferior to 14 days of antibiotics for uncomplicated gram-negative bacteremia
Gariani K et al, 2021[16]	Prospective, randomized, noninferiority **pilot** trial	93 (82% male)	65 years (range not available)	Diabetic foot osteomyelitis	Clinical Failure (30–60 days)	3 weeks comparable to 6 weeks antibiotic therapy after debridement for diabetic foot osteomyelitis