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Shorter Duration of Antibiotic Therapy for Bacterial Infections: Is the Evidence Mounting?

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Antibiotic selection pressure is one of the primary drivers of antibiotic resistance.[1] Antibiotic exposure not only increases resistance in the target bacteria when treating a bacterial infection, but also promotes resistance in non-target bacteria in the intestinal tract and other sites that are not causing the infection.[2] This leads to spreading of resistance genes to other related and unrelated bacteria.[2] Limiting exposure to antibiotics is a key strategy to prevent the escalating problem of antibiotic resistance.[3] A significant proportion of antibiotic use in the community setting is inappropriate—in particular, prescribing antibiotics to treat upper respiratory tract symptoms and acute diarrheal illness, which are predominantly viral in origin.[1,4] However, even in cases of proven bacterial infections, longer than necessary antibiotic courses are unwarranted.

"Short-course antibiotics, where possible, will be beneficial not only to reduce the risk of antibiotic resistance, but also decrease the risk of allergic reactions, C. difficile *infection and patient costs."*

Several clinical trials have established the efficacy of antibiotics by reducing mortality in various bacterial infections.[5] However, these clinical trials did not give serious consideration to precise duration of antibiotic therapy. This could be attributed to lack of incentive to pharmaceutical companies to shorten the duration of antibiotic therapy.[6] Short courses of antibiotics, where possible, will be beneficial, not only to reduce the risk of antibiotic resistance, but also to decrease the risks of allergic reactions and *C. difficile* infection, and to reduce patient costs.[3] To date, there are very limited accounts of bacterial infections where the duration of antibiotic therapy has been established in clinical trials (Table 1).[7-18] Evidence from these studies suggests that there is a substantial opportunity to limit the duration of antibiotic therapy without compromising the clinical outcome. For example, in the case of community-acquired pneumonia among patients who are hospitalized, five days of therapy were shown to be sufficient as long as patients remain afebrile for 48 hours and remained clinically stable.[9] Similarly, in women with community-acquired pyelonephritis, seven days of therapy were as efficacious as fourteen days of therapy.[14] Even among conditions such as pyogenic vertebral osteomyelitis, where duration of therapy might be prolonged up to three months, limiting the duration of therapy to six weeks was found to be successful.[18] In some instances, other interventions can help reduce the duration of the antibiotic therapy. For example, in patients with complicated intra-abdominal infections, the duration of antibiotic therapy after adequate source control (defined as a procedure where infectious foci are eliminated, factors promoting ongoing infection were controlled, and anatomical derangements were corrected) could be shortened to 3-5 days.[12] The outcomes, which included surgical-site infection, recurrent intra-abdominal infection, or death, were similar in the four-day

Table 1. Outcomes with various duration of antibiotic therapy among randomized clinical trials

Study type	Infection	Comparison	Outcome	Comment
RCT[7]	Acute otitis media in young children (6-23 months) treated with amoxicillin-clavulanic acid	5 v/s 10 days	Longer treatment	Clinical failure was more common in the short treatment group and there were no differences in emergence of antimicrobial resistance.
MA[8]	Uncomplicated acute bacterial sinusitis	3-7 days v/s 6-10 days	No difference	Similar clinical success, microbiological efficacy and relapses with both regimens. In a sensitivity analysis, adverse events were less common with the short regimen when comparing 5 vs 10 days.
RCT[9]	Hospitalized patients with community acquired pneumonia	5 days if no fever and clinically stable v/s duration determined by physician	No difference	The median duration was 10 days if the duration was determined by physicians (control group).
MA[10]	Ventilator-associated pneumonia	7-8 days v/s 10-15 days	No difference	No difference in mortality or relapse, although there was a strong trend (odds ratio=1.67) of higher risk of relapse with the short regimen based on the results of one RCT.
MA[11]	Acute exacerbation of chronic bronchitis or COPD	5 days v/s >5 days	No difference	Similar results for clinical and bacteriological cure at early (<25 days) and late follow up. The mean duration of antibiotics in long treatment groups was 8.3 days.
RCT[12]	Complicated intra-abdominal infection after adequate source control	3-5 days v/s 10 days (maximum) or until resolution of fever, leucocytosis and ileus	No difference	The median duration in the short treatment group was 4 days and in the long treatment group was 8 days.
MA[13]	Asymptomatic bacteriuria in pregnant women	Single dose v/s 4-7 days	Longer treatment	Single dose was associated with worse cure rates and low birth-weight of babies.
RCT[14]	Community-acquired acute pyelonephritis in adult women treated with ciprofloxacin 500mg BID	7 v/s 14 days	No difference	Similar clinical and bacteriological outcome 10-14 days after the end of treatment. The study included complicated (patients with diabetes mellitus or abnormalities of the urinary tract) infections. Patients with urinary catheter were excluded.

Table 1 continued

Study type	Infection	Comparison	Outcome	Comment
RCT[15]	Multidrug resistant typhoid fever in children treated with ceftriaxone	7 v/s 14 days	Longer treatment	Initial response was similar, but relapse was more common in the short treatment group.
RCT[16]	Uncomplicated cellulitis treated with levofloxacin 500mg OD	5 v/s 10 days	No difference	Participants who had abscess or no initial clinical improvement were excluded. Many patients had substantial erythema at day 5 but erythema resolved similarly in both groups regardless of the continuation of levofloxacin.
RCT[17]	Uncomplicated skin abscess (diameter <5 cm) after incision and drainage	No antibiotic treatment v/s 10 days	Longer treatment	After 20 days, the cure rate was lower in the no-treatment group if *Staphylococcus aureus* was isolated.
RCT[18]	Vertebral osteomyelitis in adults with microbiological confirmation	6 v/s 12 weeks	No difference	Similar cure rates after one year.

therapy group when compared with other groups with longer duration of therapy.

In contrast to these findings, in certain infections, shorter duration of therapy was found to be inferior. For example, in acute otitis media involving children between 6 and 23 months, five days of amoxicillin-clavulanic acid therapy resulted in more cases of clinical failure when compared to 10 days of therapy.[7] In addition, there was no increase in nasopharyngeal colonization with penicillin non-susceptible pathogens in the 10-day group. Similarly, in another study involving children with multi-drug resistant *Salmonella* Typhi bacteremia, shorter duration of antibiotic therapy with 7 days resulted in bacterial relapse in 14% of patients, whereas no cases of relapse were encountered in patients who received 14 days of therapy.[15] However, including a third group with 10 days of therapy would have been valuable. As enteric fever presents a significant burden in the Indian subcontinent, shortening to four days of therapy could lead to a substantial decrease in overall antibiotic consumption at the population level. These variable findings in the clinical trials further suggest the need for evidence to determine the correct duration of antibiotic therapy for several other bacterial infections.

Shortening the duration of antibiotic therapy without strong evidence will be a difficult task for physicians. A recent international cross-sectional survey by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) involving infection specialists (infectious disease specialists and clinical microbiologists) in 58 countries showed that the majority (64%) of them did not advise the shortest possible duration of antibiotic therapy to prescribers.[18] Efforts to conduct more clinical trials to define duration of antibiotic therapy were made more than a decade ago by professional organizations such as the Infectious Diseases Society of America (IDSA).[6] As support from the pharmaceutical industry will be minimal to conduct these trials, the role of national agencies has been recognized as critical, but progress has been disappointing. On reviewing 24,676 clinical trials classified under the "communicable diseases" category in the Clinicaltrials.gov registry between March 1 and March 31,

Table 2. Clinical trials focused on duration of antibiotic therapy

Infection syndrome	Name of the RCT	Arms	Country	Status
Bacteremia https://ClinicalTrials.gov/show/NCT02261506	Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness: A Pilot RCT (BALANCE)	7 v/s 14 days, ICU patients only	Canada (multi-center)	Completed
https://clinicaltrials.gov/ct2/show/NCT03101072	Antibiotic Durations for Gram-negative Bacteremia (PIRATE)	7 v/s 14days v/s individualized	Switzerland, France (multi-center)	Recruiting
https://ClinicalTrials.gov/show/NCT01737320	Duration of Antibiotics for the treatment of Gram-negative bacilli Bacteremia - a RCT	7 v/s 14 days	Israel, Italy (multi-center)	Recruiting
https://ClinicalTrials.gov/show/NCT02917551	BALANCE on the Wards: A Pilot RCT (BALANCE-Wards)	7 v/s 14 days, non-ICU patients	Canada (single center)	Recruiting
https://ClinicalTrials.gov/show/NCT02400268	Antibiotic Treatment Duration Comparison in Blood Stream Infection Causes by Enterobacteriaceae (SHORTEN)	7 v/s 14 days	Spain (multi-center)	Completed
https://ClinicalTrials.gov/show/NCT03005145	Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness: Randomized Controlled Trial	7 v/s 14 days	Multinational (Australia, Canada, New Zealand, Saudi Arabia)	Recruiting
Bacteriuria (Asymptomatic) https://ClinicalTrials.gov/show/NCT02575495	A RCT of Antibiotic Treatment Duration For Asymptomatic Bacteriuria After Kidney Transplantation	7 v/s 14 days	Thailand (single center)	Completed
Complicated Intra-abdominal Infections https://ClinicalTrials.gov/show/NCT03265834	Antibiotic Duration for Complicated Intra-ABdominal Infection (CABI)	< 10 days v/s 28 days	UK (single center)	Recruiting
Erythema Chronicum Migrans https://ClinicalTrials.gov/show/NCT03337932	Duration of Doxycycline Treatment in Patients With Multiple Erythema Migrans (MEM). A RCT	7 v/s 14 days	Slovenia (single center)	Recruiting
***Helicobacter pylori* Infection** *https://ClinicalTrials.gov/show/NCT01042184*	Efficacy of 10-day and 14-day Sequential Therapy Versus Triple Therapy on the Eradication of *H. pylori*	10 v/s 14 days	Taiwan (single center)	Completed

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Table 2 continued

Infection syndrome	Name of the RCT	Arms	Country	Status
Neonatal Sepsis https://ClinicalTrials.gov/show/NCT03280147	Comparison of the Efficacy of a 7-day Versus 14-day Course of Intravenous Antibiotics in the Treatment of Uncomplicated Neonatal Bacterial Sepsis: a Randomized Controlled Non-inferiority Trial	7 v/s 14 days	India (multi-center)	Not yet recruiting
Pneumonia, Bacterial https://ClinicalTrials.gov/show/NCT01554657	Five Versus Seven Day Antibiotic Course for the Treatment of Pneumonia in the Intensive Care Unit	5 v/s 7 days	USA (single center)	Completed in 2012
Scrub Typhus https://ClinicalTrials.gov/show/NCT03083197	The Scrub Typhus Antibiotic Resistance Trial (START) Comparing Doxycycline and Azithromycin Treatment Modalities in Areas of Reported Antimicrobial Resistance for Scrub Typhus	7 v/s 3 days	Thailand (multi-center)	Recruiting
Ventilator-Associated Pneumonia https://ClinicalTrials.gov/show/NCT02634411	Impact of the Duration of Antibiotics on Clinical Events in Patients With *Pseudomonas aeruginosa Ventilator-associated Pneumonia*	8 v/s 15 days	France (single center)	Recruiting

2018, we identified only 14 clinical trials in various stages that address the issue of duration of antibiotic therapy for bacterial infections (Table 2). Among these 14 trials, six focused on addressing duration of therapy for gram-negative bacteremia, of which two were completed. Other conditions—each with just one clinical trial—included asymptomatic bacteriuria among kidney transplant patients, complicated intra-abdominal infections, Erythema Chronicum Migrans, *Helicobacter pylori* infection, neonatal sepsis, pneumonia in intensive care unit patients, scrub typhus and ventilator-associated pneumonia.

Although, antibiotic resistance is recognized as a major public health problem globally, efforts to study the precise duration of antibiotic therapy for various bacterial infections seem to be moving at a slow pace. We need to get more serious about generating the evidence needed to rationalize antibiotic courses. Collaborations with national agencies, pharmaceutical companies, other funding agencies and academic research networks are urgently needed to make further progress.

Acknowledgement: *The authors thank Dr. Snigda Chukka for reviewing the Clinicaltrials.gov website to identify studies on duration of antibiotic therapy.*

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Upcoming Events

June 7-11, 2018
ASM Microbe, Atlanta, GA

June 13-15, 2018
Association for Professionals in Infection Control and Epidemiology (APIC) Annual Conference. (Minneapolis, MN. USA)

June 22-25, 2018,
5th International One Health Congress, Saskatoon Canada - with special focus on antimicrobial resistance, translational science, and recent advances in the fields of zoonoses and emerging infectious diseases.

July 14-15, 2018
4th World Congress and Exhibition on Antibiotics and Antibiotic Resistance**:** A New Era in Antibiotics Drug Development. (Barcelona, Spain)

July 22-27, 2018
Gordon Research Conference on Drug Resistance: Looking for Common Themes and Solutions in Drug Resistance for Cancer, Infectious Disease and Agriculture (Smithfield, RI, USA)

September 4-7, 2018
ESCMID/ASM Conference on Drug Development to Meet the Challenge of Antimicrobial Resistance (Lisbon, Portugal)

September 24-25
2nd Annual Summit on Antimicrobials and Drug Resistance: Antimicrobes 2018, sponsored by Allied Academies (Montreal, Canada)

October 6-14, 2018
International Course on Antibiotics and Resistance (ICARe)
The Institut Pasteur's course on advanced instruction on antibiotics and resistance that examines cutting-edge approaches for detection of resistance and antibiotic discovery, chemical optimization. (Les Pensieres, Annecy, France)

November 12-18, 2018
U.S. Antibiotic Awareness Week (formerly *Get Smart About Antibiotics Week*): CDC's annual one-week observance to raise awareness of the threat of antibiotic resistance—an international collaboration with European Antibiotic Awareness Day, Australia's Antibiotic Awareness Week, Canada's Antibiotic Awareness Week, and World Antibiotic Awareness Week

November 15-16, 2018
2018 Institut Pasteur International Network Symposium, *Combating resistance: microbes and vectors (*Paris, France)

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