The Overton window and a less dogmatic approach to antibiotics

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Summary: This viewpoint will discuss recent non-inferiority trials for infectious diseases, highlighting the value of those addressing pragmatic questions in clinical infectious diseases

This analysis summarizes a set of recent trials in infectious disease discussing innovative trials redefining previous non-evidence based “rules” for antibiotics.

Abstract

Importance: Recent trials in infectious disease have led to reconsidering traditional treatment of infectious disease—changing the duration or type of traditional antibiotics or evaluating new antibiotics for approval. These trials have used the non-inferiority trial approach. The non-inferiority trial design and recent infectious disease trials of relevance are discussed in this viewpoint.

Objective: To analyze recent trials in infectious disease and consider needs for future trials.

Design: Viewpoint related to recent infectious disease trials

Setting: Not applicable

Key words: antibiotics, bacteremia; antimicrobial stewardship

Public policy thinker Joseph Overton conceived that there are a range of ideas considered acceptable to the public. For an idea to be politically viable it needed to be within that range, which has become known as the "Overton window". The challenge for policy makers wasn't so much passing laws but moving ideas into that window. Examples include public policies that until relatively recently were unthinkable, including gay marriage or legalized marijuana in the United States. After entry into public discussion these ideas soon became law in much if not all of the US.

Medicine has many similarities to politics. Although ostensibly a scientific and objective process, only the ideas that are considered and evaluated can generate clinical evidence. As much as those of us who practice medicine would like to imagine our decisions are based on objective information, the sources and reliability of that information are limited. The rationale for many principles of antibiotic use are based on expert opinion—with "rules" such as treat bacteremia for at least two weeks, only use intravenous antibiotics for bacteremia, treat osteomyelitis for six weeks etc. Most durations of therapy relate to the obviously subjective timeline of weeks—as though microbes responded to multiples of seven days. Furthermore, many such principles were determined in an era with fewer antibiotics with limited oral bioavailability.

Antibiotic resistant bacteria have become a well-known problem in medicine, recently being named among the top 10 threats to human health by the United Nations. Strategies to maintain effective antibiotics and avoid what has been termed a "post-antibiotic era" include preserving the antibiotics we have through limiting use and developing new antibiotics. Preserving use has focused on antimicrobial stewardship, or having infectious disease experts restrict, review, or advise on judicious use based on current evidence. New evidence that changes standard practice to shorten courses of antibiotics should also prevent resistance.

Non-inferiority trials are central to both evaluating shorter or safer antibiotic courses and approval of new antibiotics.[1] Non-inferiority trials are in contrast to traditional superiority trials that are performed to statistically determine if one treatment is better than another. Although superiority trials often don't find one treatment is better, they can't be interpreted as definitely showing the two treatments are equivalent. To explain why, take the absurd hypothetical of a trial enrolling two patients that found both had the same outcome and reached the conclusion that the treatments were equivalent. Obviously more patients must be enrolled to know that both treatments are the same. The science of non-inferiority trials has developed to evaluate this by calculating a margin of difference that could be detected with the appropriate sample size. Say, treatment A is no more than 10% better or worse than treatment B. The more patients enrolled and the more common the outcome, the smaller the margin that can be detected. With more patients a margin of 10% better or worse can be reduced to 5% better or worse. Non-inferiority trials are an important development in research methods and can be rigorously performed and are important to advancing the clinical evidence base.

Beyond the epidemiological nuts and bolts of making a non-inferiority trial rigorous, there are many decisions in a non-inferiority trial that are relevant and easier for practicing physicians to assess relating to relevance and generalizability. The biggest question is what is being compared? What is in treatment A vs. treatment B? Is the comparison one we care about?

Some have advocated that non-inferiority trials should only be performed vs. a current standard of care if the new treatment has other advantages.[2] For example, is a new treatment safer or easier than the standard while offering the same physical outcome? A recent study compared initial surgery vs. physical therapy for knee arthritis with meniscal tear—in which both approaches were found to be non-inferior for knee function but physical therapy obviously has benefits over surgery.[3]

In infectious disease, non-inferiority studies have been primarily used to evaluate shorter or easier antibiotic courses or used to approve new antibiotics. [4] The use of non-inferiority for new antibiotic

approval merits attention as it is the primary approach to recent antibiotic approval. Doctors should evaluate such trials the same way they do for a non-inferiority trial of treatment options. What is being compared? Is the standard of care the standard they practice and if treatments are non-inferior, what additional benefits come from the new treatment? For some new antibiotics the potential patient benefits are obvious, such as easier administration say with weekly dalbavancin for Acute bacterial skin and skin structure infection (ABSSSI)[5] or oral vs. intravenous treatment with linezolid for MRSA.[6]

A goal of non-inferiority antibiotic approval that is specific to infectious disease, is the goal of having more antibiotics approved and available that can then be primarily used "off label" for other reasons. For example, ceftazidime-avibactam was approved for community-acquired intraabdominal infection (cIAI)[7] or community-acquired urinary tract infection (cUTI),[8] but the primary interest is for off label use for any carbapenem-resistant *Enterobacteriaceae* (CRE) infection, given the in-vitro activity of ceftazidime-avibactam against most CRE. Another drug, ceftaroline was approved for cIAI and ABSSSI but clinician experience and observational studies suggest it may be effective for MRSA bacteremia.[9] Infectious disease is special in that many difficult infections like CRE, are rare and occur in complex patients, making specific trials very difficult—as demonstrated in the CARE (Combating Antibiotic Resistant *Enterobacteriaceae*) trial that was unable to complete enrollment for CRE infections.[10]

As clinicians, we must evaluate each new antibiotic approved to see if it holds potential benefits over current practice and holds value to our patients.

Recent infectious disease non-inferiority trials have questioned longstanding dogma and expanded the Overton window for what is acceptable to the medical community. The Partial Oral Endocarditis Treatment (POET) trial in Denmark studied 400 patients with endocarditis.[11] They included typical left sided endocarditis with multiple organisms including native and prosthetic valves and randomized patients to oral therapy for part of their treatment course versus a traditional complete

intravenous course. About half the days of antibiotic therapy were given orally. Although standard in many diseases, use of oral antibiotics for endocarditis has been considered inferior and intravenous antibiotics for four to six weeks the standard of care. The POET trial found no difference between groups, with a small absolute change favoring oral therapy (9% vs. 12% with death, failure or complications). The Oral Versus IntraVenous Antibiotic treatment for bone and joint infections (OVIVA) trial in the United Kingdom took a similar approach to antibiotics for bone and joint infections, randomizing patients to oral antibiotics following no more than seven days of intravenous antibiotics.[12] Again, they found no difference in failure rates in this non-inferiority trial (14·6% failed intravenous antibiotics vs. 13·2% failed oral therapy). Notably, catheter complications were more common in the intravenous group (9·4% vs. 1·0%). This study included osteomyelitis complicating diabetic foot ulcers which is a common condition and findings likely apply to many patients. Finally, in Israel and Italy, investigators without external funding examined the long-held dogma that bacteremia requires two weeks of antibiotics.[13] They studied patients with common infections like urinary tract infection (UTI) and a blood isolate positive for a gram-negative bacterium. This study found no difference in one versus two weeks of antibiotics and patients, in fact, reported a return to baseline status sooner if patients were randomized to one week of antibiotics.

These studies are important. All were non-inferiority trials with large sample sizes capable of finding reasonable non-inferiority margins; these were sample size 1054, margin +/- 7.5%,[12] sample size 400, margin +/- 10%,[11] sample size 604, margin +/- 10%,[13] They demonstrated antibiotics can be equally effective and safer with a shorter, predominantly oral course. Similar trials a few years ago upended management of appendicitis by showing antibiotic therapy has similar outcomes to surgery,[14] or being more conservative with blood transfusions improves mortality.[15] These relatively inexpensive studies exploring standard practice will likely expand Overton's window for how we use antibiotics. Future trials should explore details related to this management—are oral antibiotics safe in all patients with all

organisms? Does the type of antibiotic matter? But these trials took the important initial step of making these options reasonable to consider.

This is in contrast to recent antibiotic approval of non-inferiority trials for omadacycline, the tetracycline antibiotic appeared in two articles that were the basis for FDA approval.[16,17] The first trial demonstrated omadacycline was non-inferior to linezolid for cellulitis used for seven to 14 days.[16] The other trial compared omadacycline to moxifloxacin for community acquired pneumonia used for seven to 14 days duration.[17] Both trials found omadacycline to be non-inferior in long duration compared to a non-first line drug for pneumonia or cellulitis. Questions relating to the long duration of antibiotic treatment, a non-significant doubling of deaths in the pneumonia study (8 vs. 4), comparison to second line drugs, lack of novel mechanism without any advantages to the drug will likely relegate omadacycline to become the next tigecycline—FDA approved but rarely used and far from innovative or needed. There are lessons from these recent studies:

Addressing important immediate clinical issues that are common with little clinical evidence has provided a strong return on investment. Shifting towards oral antibiotics and shorter courses, has an obvious benefit of reduced risk and burden on the patient, in addition to reducing costs.

The expansion of the Overton window for antibiotics with evidence showing it is safer and equally effective to use shorter courses of antibiotics or oral instead of intravenous antibiotics may change the landscape of infectious disease and post-acute care medicine. We can expect fewer peripherally inserted central catheter (PICC) lines and management of antibiotics at home by nurses, in an infusion center by an infectious disease doctor or at a nursing home for patients unable to be cared for at home. Antibiotics that are easier to administer at a lower cost are clearly higher value medicine.

The POET, OVIVA and bacteremia studies required thoughtful regulatory oversight that accepted evaluation of less aggressive treatment than the current standard of care. Institutional review board

(IRB) oversight is institution dependent and often risk adverse. IRBs are often unwilling to consider doing less for patients than a perceived standard of care, and trials of less aggressive management required evaluation of the evidence base for a standard of care to determine if an alternative approach was worth studying.

Newly approved antibiotics that are non-inferior to a standard antibiotic should be evaluated in terms of other benefits—are they easier or safer to use? Do they have a potential benefit for a rare disease like CRE that can't be easily studied?

The trials of Iverson, Li, and Yahav promote a pragmatic approach to infectious diseases demonstrating the value of addressing pertinent clinical questions.[11–13] Physicians, research ethicists and policy makers and research funders should take note. Better care is possible at lower costs if we invest wisely in relatively simple studies of how to best use the tools we have. The potential to consider oral antibiotics for osteomyelitis and endocarditis or shorter courses for serious infections expands Overton's window for antibiotic use. These approaches becoming acceptable is likely to immediately change clinical practice with antibiotics and spur further studies to examine details about the shortest and safest way to use antibiotics. These studies achieved the highest goal of clinical research—to improve real world patient care for those suffering from serious illness.

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