Tingsgård and colleagues performed a cohort study using a target trial emulation analysis to assess whether an early transition to oral antibiotics (ie, early oral switch [EOS]) was an effective alternative to a complete intravenous antibiotic course in adults with uncomplicated bloodstream infection (BSI) due to gram-negative bacteria in Denmark. They concluded that EOS was safe and effective on the basis of similar 90-day all-cause mortality in the cohort treated with EOS and the cohort that received prolonged intravenous antibiotic treatment. This conclusion is consistent with that reported in a recent randomized clinical trial (RCT), which showed that when using a composite endpoint of treatment failure (death, need for additional antimicrobial therapy, microbiological relapse, or infection-related readmission at 90 days), EOS was not inferior to continuing oral therapy. Nonetheless, further data are required to determine the ideal timing of EOS and to identify the most effective oral agents for this strategy. This includes investigating whether β-lactam antibiotics are adequate as oral step-down agents in treating these infections, as opposed to fluoroquinolones or trimethoprim-sulfamethoxazole. As Tingsgård et al noted, another large multinational RCT is underway addressing some of these questions, and a US-based RCT on EOS is expected to commence recruitment in 2024.

Tingsgård and colleagues have also recently published a comparative effectiveness cohort study using target trial emulation analysis to assess whether short antibiotic treatment duration (ie, 5-7 days) had similar 90-day mortality to longer antibiotic treatment course (ie, 8-14 days) for BSI due to gram-negative bacteria. Three RCTs had already found that short-course treatment is as effective as longer antibiotic courses, although larger RCTs have yet to report results.

Clinicians in all fields rely on high-quality data with which to make diagnostic and management decisions. Since observational studies using a rigorous methodological approach, such as the study by Tingsgård et al, have found the same conclusions as RCTs, can clinicians bypass the need for RCTs and simply base their decision-making on observational data? With regard to antibiotic use, there is often a feeling that RCTs are too difficult to perform on the basis of myriad issues, such as lack of funding, difficulty with timely enrollment, and inability to tease apart poor outcomes related to underlying disease vs inadequate effectiveness of the antibiotic under study. Much of this perception is likely related to the failure of the antibiotic market and the inability of pharmaceutical companies to attract sufficient capital to perform large RCTs. Yet more than 100 clinician-initiated RCTs evaluating antibiotic use have been performed in the last decade. RCTs of antibiotic use strategies enrolling more than 1000 patients in each treatment group have recently been completed. A large multicontinental platform trial of treatment strategies for *Staphylococcus aureus* BSI is well underway. Clinical trial networks studying antibiotic use are running in the US, Canada, Australia, New Zealand, Europe, and Asia. An RCT of antibiotic choices has been successfully conducted in the US in which waiver of informed consent was approved by the relevant institutional review board and in which randomization assignment was embedded within the electronic health record.

It is our belief that the use of observational data to compare different antibiotic use strategies should primarily be used when data from RCTs are not available. Even with the most modern methods of causal inference, confounding may still occur, leading to erroneous conclusions. The use of observational data should be hypothesis-generating rather than confirming the results of RCTs. The term *real world* is often used synonymously with *observational*, as though RCTs cannot provide...
real-world evidence. Certainly, RCTs used to gain regulatory approval for a new antibiotic typically have numerous exclusion criteria. However, most clinician-initiated RCTs are pragmatic, have few exclusion criteria, and lead to generalizable conclusions. Applying the real-world label to observational data does not somehow make it more valuable to clinicians than data from RCTs, nor does it eliminate confounding.

Tingsgård and colleagues\(^1\) use their application of target trial emulation analysis to assess very practical questions regarding antibiotic use. These methods should be the preferred option when observational data are used to compare the effectiveness of treatment strategies. Yet, we favor data from RCTs when it comes to making evidence-based prescribing decisions.

**REFERENCES**


