Burst Case Scenario: Why Shorter May Not Be Any Better When It Comes to Corticosteroids

Seventy years ago, Phillip Hench and colleagues (1) described striking clinical improvement in 21 patients with rheumatoid arthritis who were given cortisone. The same article described in detail "certain side effects" that affected most patients, including fluid retention, hypertension, psychiatric disturbances, cushingoid habitus, and hyperglycemia. Hench's discovery was touted as a "miracle cure" for devastating chronic inflammatory conditions, and it led first to prevalent use of long-term, high-dose corticosteroids, then to increasing recognition of their severe adverse effects. Soon, many wondered if such "treatment with cortisone [was] worth while" (2), given its unfavorable toxicity profile.

This year, clinicians will prescribe courses of oral corticosteroids to three quarters of patients with chronic inflammatory disorders (3) and up to 17% of the general population (4). Most of these will be short "bursts" of 1 or 2 weeks, typically prescribed for common ailments like upper respiratory tract infections, bronchitis, skin rashes, and low back pain (5, 6). Many clinicians believe that such bursts are harmless, a position backed by years of data connecting exposure duration to toxicity. Several recent studies, however, have challenged this assumption, showing increased rates of sepsis, heart attack, stroke, venous thromboembolism, and fracture among patients receiving oral corticosteroids for fewer than 30 days (5, 7). Although exposure duration in these studies was low (a median of 6 days in 1 study) (5), the authors did not comment on how the 1- to 2-week bursts we most commonly prescribe may have contributed to their results.

Yao and colleagues (8) are the first to our knowledge to report specifically on the potential harms of 14 or fewer days of oral corticosteroid exposure. In their retrospective analysis of 15 million patients in Taiwan's National Health Insurance Program, the investigators evaluated the relationship between these brief exposures and 3 adverse events (AEs) associated with corticosteroids: gastrointestinal bleeding, sepsis, and heart failure. Twenty-five percent of the population received corticosteroids during the study period. Among these patients, mean age was 38 years, and 85% had no baseline comorbid conditions. More than half of corticosteroids were prescribed for acute contact dermatitis, rhinosinusitis, laryngitis, pharyngitis, bronchitis, or tonsillitis. Corticosteroid bursts were associated with significantly increased rates of all 3 AEs, despite a median exposure of just 3 days. Rate increases were highest 5 to 30 days after exposure but remained elevated after 3 months. Absolute risk differences were 10.3, 0.1, and 1.0 per 1000 patient-years for gastrointestinal bleeding, sepsis, and heart failure, respectively. These absolute risk increases were similar in patients with and without comorbid conditions, meaning that the potential for harm was not limited to persons at high risk for these AEs.

With more than 4 million exposed patients, this is the largest study to date examining the risks of short-term corticosteroid use. The large sample size allowed investigators to detect small but significant increases in 3 major AEs associated with corticosteroids. On the basis of the risk differences reported, the 4 million patients exposed to corticosteroid bursts experienced 41 200 gastrointestinal bleeding events, 400 cases of sepsis, and 4000 cases of new heart failure per year that were directly attributed to this brief exposure. Of note, these increases remained significant among young, otherwise healthy patients, most of whom received corticosteroids for self-limited conditions.

Studies using administrative data must deal with residual confounding, which in this case might include lifestyle factors like tobacco or alcohol use. The investigators addressed this by using a self-controlled case series design, which compares each patient's event rates immediately before versus immediately after corticosteroid exposure (5). The presence or severity of underlying conditions may still have increased both corticosteroid bursts (the exposure) and risk for AEs (the outcome). Future studies will also be needed to assess the validity of these findings in other populations, evaluate associations between bursts and other corticosteroid-associated AEs (such as major cardiovascular events, venous thromboembolism, and fractures), evaluate how burst dose affects AE frequency, and further examine how age and comorbid conditions modify the risks of burst use.

Medication-related risks for AEs can, of course, be outweighed by major treatment benefit. However, this study and prior work show that corticosteroid bursts are frequently prescribed for self-limited conditions, where evidence of benefit is lacking. In patients with severe chronic inflammatory conditions, treating acute flares with corticosteroid bursts may prevent disability, preserve function, and maintain quality of life. In contrast, bursts prescribed for self-limited conditions confer no long-term benefit and may not even reduce symptom duration or severity (9). The investigators also emphasize that corticosteroid bursts pose harm to young, otherwise healthy patients. Although many providers already avoid corticosteroids in elderly patients and those with comorbid conditions, prescribing short bursts to "low-risk" patients has generally been viewed as innocuous, even in cases where the benefit is unclear. However, Yao and colleagues (8) provide evidence that this practice may risk serious harm, making it difficult to justify in cases where corticosteroid use lacks evidence of meaningful benefit.

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As we reflect on how to respond to these findings, it is useful to note the many parallels between use of corticosteroid bursts and that of other short-term medications, such as antibiotics and opiates. All of these treatments have well-defined indications but can cause net harm when used—as they frequently are—when evidence of benefit is low. Like those for antibiotics and opiates, prescribing patterns for corticosteroids vary widely (3) and are greatly influenced by provider preference (10). We can thus conceive of a "corticosteroid stewardship" model of targeted interventions that aims to reduce inappropriate prescribing.

We have known for nearly a century that long-term corticosteroids are both effective and toxic. However, we commonly use short corticosteroid "bursts" for minor ailments despite a lack of evidence for meaningful benefit. We are now learning that bursts as short as 3 days may increase risk for serious AEs, even in young and healthy people. As providers, we must reflect on how and why we prescribe corticosteroids to develop strategies that prevent avoidable harms.

Beth I. Wallace, MD, MSc
Akbar K. Waljee, MD, MSc
Center for Clinical Management Research at VA Ann Arbor Healthcare System and Institute for Healthcare Policy and Innovation at Michigan Medicine
Ann Arbor, Michigan

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Corresponding Author: Beth I. Wallace, MD, MSc, Michigan Medicine, 300 North Ingalls Building, Room 7C27, Ann Arbor, MI 48109-5422; e-mail, brennerb@umich.edu.

Current author addresses are available at Annals.org.

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Current Author Addresses: Dr. Wallace: Michigan Medicine, 300 North Ingalls Building, Room 7C27, Ann Arbor, MI 48109-5422.
Dr. Waljee: VA Ann Arbor Healthcare System, 2215 Fuller Road, Gastroenterology 111D, Ann Arbor, MI 48105.