



Balancing the myths of corticosteroid therapy

No class of drug has more mythical attributes, interfaces with different medical specialties, or clinical street lore than corticosteroids. As posited in the 1978 satirical novel *The House of God*,¹ no one acutely ill should die in the hospital without consideration to receive some “roids.” The striking benefits of corticosteroid treatment for many inflammatory conditions are well accepted. Demonstration of their efficacy in treating rheumatoid arthritis resulted in a Nobel prize in physiology and medicine being awarded in 1950 to Hench, Kendall, and Reichstein.

Steroids have been a linchpin treatment of inflammatory disease since then. There has been recognition for their lifesaving potential, and also for toxicities associated with their use. When I discuss treatment options with my patients, I emphasize that the newer nonsteroid immunosuppressive drugs have potential toxicities that are indeed scary and *may* occur, but that corticosteroids, due to their hormonal activity, have adverse effects that *will* occur with ongoing use. Strategies to limit these adverse effects include alternate-day therapy (this works for a few diseases), local application to limit systemic effects (inhalational, intralesional, and intra-articular), and “pulse dosing” utilizing a super-high dose for a few days. The last has achieved, appropriately or not, an iconic place in established as well as “Hail Mary” treatment paradigms for a host of inflammatory conditions.

Pulse dosing, several days of as much as a gram of intravenous methylprednisolone, was introduced around 1970 to treat the early rejection of transplanted kidneys.² Mechanistic rationales included potential lytic effects of high doses on lymphocyte subsets, effects on the time course of lymphocyte migration, and provision of a time-limited intense treatment course to minimize adverse effects of long-term corticosteroid therapy. With our increasing but still incomplete understanding of how these drugs work, it seems possible that ultra-high doses of corticosteroids may have direct membrane-active effects in addition to their inhibitory effects on nuclear transcription mediated by nuclear factor kappa B and other steroid-responsive nuclear factors. But a substantial clinical benefit of pulse dosing has yet to be documented in a rigorous way for most conditions for which it is utilized. There remains the fear of “What if we didn’t give enough?”—while at the same time, clinical investigators are evaluating the necessity of traditional high doses given for induction therapy in the treatment of inflammatory diseases including severe ANCA-associated vasculitis.³

Clearly the best way to limit the adverse effects of corticosteroid therapy is to limit their use. There has been an aggressive movement within rheumatology and nephrology to limit the use of corticosteroids in the management of several immunologic conditions, including renal transplantation, lupus nephritis, ANCA-associated vasculitis, and giant cell arteritis. This strategy is bolstered by recent publications indicating toxicity of even low-dose corticosteroid use over time, as well as the apparent lack of additional therapeutic benefit provided by higher vs lower doses of corticosteroids for systemic vasculitis. The availability of a structured approach to track glucocorticoid toxicity⁴ in clinical trials (and in practice) should provide an ongoing impetus to further this movement.

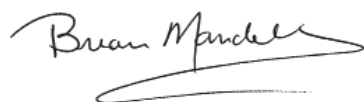
All clinicians share concern for increased risk of infections in patients treated with corticosteroids—from the annoying yet manageable oral candidiasis to potentially life-threatening pulmonary and systemic fungal infections, and the delayed recognition of deep-seated infections. In

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addition, the administration of corticosteroids increases the peripheral neutrophil count and can suppress fever, thus complicating diagnostic and management decisions. So it has seemed almost paradoxical to be purposefully and effectively treating certain infections with corticosteroids (in addition to providing appropriate anti-infective agents). And yet there is reasonable evidence from clinical trials to support corticosteroid cotherapy in the management of selected patients with severe bacterial or pneumocystis pneumonia, bacterial meningitis, tuberculous pericarditis, bacterial native joint infections, and COVID-19, with significant pulmonary involvement.

A decades-long debate continues over the use of corticosteroids in sepsis. Forty years ago, a series of papers presented dramatic data showing the lifesaving effect of corticosteroids (with gentamicin) when provided very early following the administration of a lethal dose of *Escherichia coli* to baboons.⁵ Since then, animal studies and clinical trials have attempted to determine the efficacy or detriment of corticosteroid use in patients with sepsis, sepsis syndromes, and associated parenchymal injury like adult respiratory distress syndrome.

In this issue of the *Journal*, Pastores⁶ very nicely reviews the data and discusses his approach to the use of steroids in sepsis and the acutely ill. It seems for the moment that the “fat man” and colleagues from *The House of God* were correct: “roids” for the acutely ill may indeed be warranted, for the short term, with questions still to be answered regarding appropriate dosing and precise patient selection.



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1. Shem S. *The House of God: A Novel*. New York: R. Marek Publishers, 1978.
2. Kountz SL, Cohn R. Initial treatment of renal allografts with large intrarenal doses of immunosuppressive drugs. *Lancet* 1969; 1(7590):338–340. doi:10.1016/s0140-6736(69)91299-9
3. Walsh M, Merkel PA, Peh CA, et al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. *N Engl J Med* 2020; 382(7):622–631. doi:10.1056/NEJMoa1803537
4. Stone JH, McDowell PJ, Jayne DRW, et al. The glucocorticoid toxicity index: measuring change in glucocorticoid toxicity over time. *Semin Arthritis Rheum* 2022; 55:152010. doi:10.1016/j.semarthrit.2022.152010
5. Hinshaw LB, Beller-Todd BK, Archer LT, et al. Effectiveness of steroid/antibiotic treatment in primates administered LD100 *Escherichia coli*. *Ann Surg* 1981; 194(1):51–56. doi:10.1097/0000658-198107000-00009
6. Pastores SM. Steroids in the acutely ill: evolving recommendations and practice. *Cleve Clin J Med* 2022; 89:505–511. doi:10.3949/ccjm.89gr.22002