EDITORIAL

Steroid use in critically ill septic patients: acknowledging the uncertainty*

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If you happen to be a critical care physician who was practicing about 25 years ago, you will remember when all our septic shock patients were receiving high-dose intravenous steroids – sometimes in excess of 2 g of methylprednisolone per day. Later, a series of meta-analyses demonstrated that this management did not benefit and likely harmed patients[1]; for the next 10 years, steroids went into hibernation. Our interest in steroids was reignited by studies suggesting that smaller dose of steroids for a longer period of time led to a faster resolution of vasopressors dependency[2] and, in patients with a relative steroid deficiency, even to a mortality benefit.[3] The subsequent CORTICUS (The Corticosteroid Therapy of Septic Shock) study,[4] reporting no benefit and possible harm, dampened the enthusiasm and influenced the 2008 clinical practice guidelines from the Surviving Sepsis Campaign (SSC) that made a weak recommendation for steroids, and suggested their use be restricted to patients whose shock is poorly responsive to vasopressors.[5]

Now we face a meta-analysis – as good as it gets – written with full cooperation of the authors of the primary studies and with access to unpublished information.[6] The authors report that 12 randomized trials the use of low-dose steroids for at least 5 days reduced mortality (relative risk [RR] 0.84, 95% confidence interval [CI] 0.72–0.97, P = 0.02) and urge more liberal use of steroids in all patients receiving vasopressors. How should clinicians respond to this potentially confusing situation?

Understanding the source of these differences may help us address the issue. The new meta-analysis shows a slightly smaller effect than the summary pooled estimate with which SSC was presented (RR 0.87 vs. 0.85), but because new information coming from recently published studies was included, it shows a slightly narrower CI (0.72–0.97 vs. 0.60–1.06). The additional data has pushed the P value below the magic 0.05, and thus the upper boundary of the 95% CI below an RR of 1.0, thus apparently excluding no effect. Does that explain the difference in recommendations?

Probably it does – in part. But there appears to be another difference in interpretation. The CORTICUS trial, which was designed specifically to address the effect of steroids among patients less sick than in a previous French trial, suggested no mortality benefit. This raises the possibility that in the spectrum of patients with sepsis, from those responsive to fluid resuscitation alone to those resistant to fluid and vasopressors, only the more severely ill benefit from steroids. Applying standards for believing such a subgroup effect[7] we note this as one of only three a priori hypotheses with a specified direction, a credible biological rationale, and a substantial difference in effect unlikely to occur by chance (P = 0.06 in the current author's regression analysis based on control group risk of dying). It is, however, much weaker because it is based on between-study differences – an individual patient data (IPD) meta-analysis would be required to definitively establish or refute the hypothesis.

Both SSC and the current authors give credibility to this hypothesis in that they restrict their recommendations to those with more severe sepsis – though the chosen threshold differs. They both, however, acknowledge the underlying uncertainty related to heterogeneity of findings in different trials and therefore rate down the quality of the evidence from high to moderate. SSC rated down further to low-quality evidence on the basis of imprecision (wide CIs).

There may be a further reason for differences in recommendations, and that is intellectual conflict of interest. Investigators are in general partial to the results of their own trials, and the investigators of the original studies (though with

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a different mix in SSC and the meta-analysis) were prominent in both settings.

This consideration raises the issue of who should be making recommendations, a process that involves the final judgments of evidence interpretation, and weighing the desirable and undesirable consequences of an intervention and associated uncertainty. Should this be part of a formal process – typically a guideline panel – or should it be part of the mandate of those conducting systematic reviews? If restricted to individuals involved in a formal decision-making process, should those with substantial intellectual or financial conflicts be excluded from the process of making recommendations?[8] Human beings, and physicians are no exception, have a natural preference for certainty over uncertainty. In addition, we have a tendency to see the world in terms of black and white, and actions as right or wrong. Further, we have a powerful inclination to get emotionally invested in our ideas, leading to polarization and potentially acrimonious debates.

These characteristics serve us poorly in a world of uncertainty – an uncertainty that is prominent in medical decision making. The lack of certainty invites probabilistic reasoning. Decisions require considering the impact of different options on a variety of outcomes, and estimating the probabilities with which such outcomes may occur. The evidence (data) at our disposal provides us with estimates of those probabilities, and with an indication of the level of confidence we can place in those estimates.

The implicit uncertainty in this process is by no means limited to the steroid-in-sepsis debate, those witnessing current discussions regarding use of long-acting β-agonists in asthma[9] or proton-pump inhibitors in patients taking aspirin and clopidogrel[10] recognize the level of uncertainty and consequent differences of opinions.

The responsibility of authors of systematic reviews and meta-analyses is to summarize the data and to make inferences regarding the quality of evidence. Whether the authors of systematic reviews should take the further step of assuming the responsibility for providing recommendations, rather than leaving that task to formal processes such as guideline panels, is open to question. In this case, the authors state that "corticosteroids should be considered at a daily dose of 200 to 300 mg of hydrocortisone (or equivalent) as intravenous bolus or continuous infusion. Treatment should be given at full dose for at least 100 hours and only in adults with vasopressor-dependent septic shock." The Cochrane Collaboration states that its reviewers are to present the evidence and its interpretation and to go no farther – specifically, they are not to make recommendations. Why might this be?

How are we to interpret the statement that corticosteroids "should be considered"? Some recommendations are based on high-quality evidence showing consistent and large beneficial treatment effects with minimal undesirable consequences. Others are based on either lower-quality data (due, for example, to less than optimal methods or heterogeneity in results) or evidence that suggests a close balance between the beneficial and negative effects of available management strategies. Clinicians should know which of these situations they are facing.

Both the systematic review under consideration and the SSC guidelines rate the quality of evidence using the GRADE system; the SSC, but not the review, also uses GRADE for communicating the strength of recommendations.[11] Though the systematic review authors support steroid use, they point out and highlight the importance of a major negative study[2]; they mention the ongoing conduct of several studies of steroids in septic syndromes (implicitly acknowledging some remaining doubt regarding important benefit); mention (though only briefly) that in their meta-regression studies with higher vs. lower control group mortality were associated with larger effect size; and ultimately rate the evidence as moderate quality despite coming from well-conducted randomized controlled trials. Perhaps their "should be considered" statement reflects this uncertainty.

One role of clinical practice guidelines, at least when using GRADE, is to explicitly convey the strength of recommendations. The SSC recommendations regarding the use of steroids were thus structured in a way designed to reflect the degree of uncertainty. The readers of SSC guideline could note that the panel failed to agree on the recommendation, and the decision required a vote. All recommendations regarding steroid were categorized as "weak", with the associated wording "we suggest" rather than "we recommend". The message the SSC was conveying was that although the panel believed it likely that giving steroids to patients with difficult to control shock would lead to overall benefit, and that they believed it unlikely that steroid administration would lead to overall benefit in those with less severe sepsis, they were not confident about either judgment.

Making evidence-based recommendations involves a series of subjective judgments, some of which (e.g., deciding which studies should be included in the meta-analysis) are liable to be more reproducible than others (deciding on the credibility of a sub-group analysis). What level of inconsistency is too high? How to translate small or imprecise benefits into clinical decisions? Those judgments are important not only in formal recommendations, but also in the decision-making process at the bedside.

Which brings another set of questions – whose judgments should those be? Should we communicate our uncertainty to the most interested, namely the patients and their families? We do it in some but not all areas of uncertainty. Informal talk to our colleagues reveals that our patterns of talking to patients about benefits and potential downsides of different interventions (say, in

patients with septic shock, activated protein C or right heart catheterization) differ considerably.

It is difficult to admit that we are not certain, difficult in interactions with patients, families, learners, ourselves. Even when we know the reasons for disagreement and the fact that alternative interpretations are reasonable, we may feel more comfortable pretending that we know the underlying truth. Nevertheless, to the extent that we can abandon the black-and-white world in which we are prone to live, conflicts diminish and shared decision making (both on guideline panels and at the bedside) becomes easier.

Considering the uncertainties that remain in the use of steroids in septic patients, what are the implications for further research and for clinical practice? Agreeing broadly with the systematic review authors' research agenda, we would like to emphasize the importance of collecting reliable data regarding the severity of patients' illness, and the desirability of an IPD meta-analysis. Such an analysis is likely to resolve, or at least inform, the issue of whether steroid effects vary across severity of sepsis. In the meantime, it is important to acknowledge that reasonable people may reach different conclusion, to recognize why our judgments differ, and to try and become more comfortable living in the world of uncertainty.

REFERENCES

1 Cronin L, Cook DJ, Cartlet J, et al. Corticosteroids treatment for sepsis: a critical appraisal and meta-analysis of the literature. Crit Care Med. 1995; 23: 1430-1439.

2 Bollaert PE, Charpentier C, Levy B, et al. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. Crit Care Med. 1998; 26: 645-650.

3 Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA. 2002; 288: 862-871.

4 Sprung CL, Annane D, Keh D, et al; CORTICUS Study Group. Hydrocortisone therapy for patients with septic shock. N Engl J Med. 2008; 358: 111-124.

5 Dellinger RP, Levy MM, Carlet JM, et al; International Surviving Sepsis Campaign Guidelines Committee. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med. 2008; 36: 296-327.

6 Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids in the treatment of severe sepsis and septic shock in adults. A systematic review. JAMA. 2009; 301: 2962-2375.

7 Guyatt G, Wyer P, Ioannidis J. When to believe a subgroup analysis. In: Guyatt G, Rennie D, Meade M, Cook D, eds. Users' guides to the medical literature: a manual for evidence-based clinical practice. McGraw Hill; 2008.

8 Hirsh J, Guyatt G. Clinical experts or methodologists to write clinical guidelines? Lancet. 2009; 374: 273-275.

9 Drazen JM, O'Byrne PM. Risks of long-acting beta-agonists in achieving asthma control. N Engl J Med. 2009; 360: 1671-1672.

10 Juurlink DN, Gomes T, Ko DT, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. CMAJ. 2009; 180: 713-718.

11 Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008; 336: 924-926.