To the Editor: Putting guidelines into the public arena for debate is an excellent idea, and Rheeder and Oosthuizen1 should be heartily commended for doing so with their guideline on hyperglycaemic emergencies.

Bicarbonate therapy in acidosis has been debated for decades. Most review articles describe its use as controversial, with many appearing to avoid too definitive a stand but eschewing its use in moderate diabetic ketoacidosis (DKA) although espousing it if the pH is below some magic figure between 7.2 and 6.9. Presumably the reasoning is that although proof of benefit may be lacking in less severe cases, there is little to be lost in more severely acidic patients. This makes the unfounded assumption that benefit of treatment accrues linearly with deviation from normal. If bicarbonate use happens to be clinically detrimental (even though pH improves) then it is conceivable that harm might be greatest in those with lowest pH.

The problem for most guideline writers is the evidence base. If the evidence is strong it is relatively easy to make a recommendation about best practice, but in that situation a guideline is redundant. Guidelines are of most use where the evidence is weak — optimistically, they serve to reflect a ‘safe’ path taken by others with greater experience. More cynically, they pander to a commonly held belief that you can’t be far wrong if you move with the herd, a lesson seldom reviewed by less observant antelope.

A Medline search on ‘ketoacidosis and bicarbonate’ back to 1966 yielded only four randomised controlled trials on the subject. This was a slew of retrospective cohorts tagging along in a blaze of biases. Although Medline searches may miss nearly half of relevant publications, it is hoped that one of the posse of derivative reviewers would have encountered (and waxed lyrical about) any further trials not indexed there. The total number of patients (Table I) exposed to adequately randomised experimentation on this subject in these trials is less than 100. Some trials were astoundingly short (2 hours!) or quite frugal when it came to recruitment (20 patients).

Management recommendations in multiple authoritative sources are therefore based on personal experience and a gloomy literature of short-duration underpowered trials with surrogate outcomes and no hard clinical endpoints. The trials demonstrated that it is possible to change pH if you add enough alkali, an observation familiar to most chemistry students but of unclear clinical relevance. On the other hand, lack of demonstration of clinical benefit in underpowered trials may also generate a type II error where small real advantages are overlooked.

Today, a manufacturer touting bicarbonate as a clinically beneficial new therapy would probably struggle to get the product registered using the available evidence.

What is needed, and what funding sources are reluctant to supply for such an old medication, is one or more high-quality adequately powered trials with clinically meaningful endpoints. In the face of growing disquiet in the literature about potential harms of bicarbonate2 in acidosis in general, and inadequate

### Table I. Randomised controlled trials of bicarbonate therapy in diabetic ketoacidosis

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number given placebo</th>
<th>Number given bicarbonate</th>
<th>Primary outcome</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutterman et al.3</td>
<td>24</td>
<td>12</td>
<td>Difference in mean pH at various times</td>
<td>Unusual randomisation method, varying insulin doses</td>
</tr>
<tr>
<td>Hale et al.4</td>
<td>32</td>
<td>16</td>
<td>Mean pH rise</td>
<td>Study follow-up only lasted 2 hours</td>
</tr>
<tr>
<td>Morris et al.5</td>
<td>21</td>
<td>10</td>
<td>Time to pH &gt; 7.3</td>
<td>Unblinded. Controls sicker?</td>
</tr>
<tr>
<td>Gamba et al.6</td>
<td>20</td>
<td>9</td>
<td>Rate of rise of pH</td>
<td>Blinded, placebo-controlled but still too small, and surrogate endpoints</td>
</tr>
</tbody>
</table>
demonstration of efficacy, an alternative departure point might be to abstain from recommending its use at all in DKA until there is clearer evidence of clinical benefit.

A Parrish
Cecilia Makiwane Hospital
East London


Rheeder and Oosthuizen reply: We thank Dr Parrish for his insightful comments regarding bicarbonate therapy in the management of diabetic ketoacidosis (DKA). The guideline we use in Pretoria is based on the position statement issued by the American Diabetes Association.1 The authors of that position statement are in full agreement with Dr Parrish: ‘Prospective randomized studies have failed to show either beneficial or deleterious changes in morbidity or mortality with bicarbonate therapy in DKA patients with pH between 6.9 and 7.1. No prospective randomized studies concerning the use of bicarbonate in DKA with pH values < 6.9 have been reported.’ While the position statement on the management of diabetic nephropathy2 grades recommendations according to level of evidence, the hyperglycaemic emergencies position statement does not do so. Even though evidence-based management in emergency medicine is desirable, ethical issues regarding informed consent and the need for sufficient numbers of participants (of a relatively rare condition) are some of the obstacles trialists need to overcome in order to provide this evidence. Most experts would agree on giving bicarbonate if the pH is less than 7.0 in DKA. We are in full agreement with Dr Parrish that at best this is level 5 evidence (expert opinion without explicit critical appraisal, or based on physiology, bench research or ‘first principles’).3 Whether this recommendation should be left out of guidelines until clear evidence of benefit is available is a matter of judgement of potential harm versus benefit.