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Reply

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To the Editor

Our criteria for the diagnosis of common variable immunodeficiency (CVID) in “international consensus document (ICON): common variable immunodeficiency disorders”¹ differ from those recently proposed by Ameratunga et al.^{2,3} Some of these differences are semantic. For example, we consider a diagnosis of CVID to be “definite” if the criteria are met, whereas Ameratunga et al consider such a diagnosis to be “probable” at best, because they do not consider a nonmolecular diagnosis to have sufficient specificity. We disagree with this position. Our goal was to establish consensus diagnostic criteria that constitute a definite diagnosis of CVID with the knowledge and information in hand. As new knowledge is acquired, diagnostic criteria will evolve and will be reinterpreted.

Other differences in the 2 sets of diagnostic criteria are substantive and will be further discussed here. One difference is a requirement for low IgG defined by 2 standard deviations (SD) below local laboratory norms (ICON) versus IgG < 5 g/L for all adults (Ameratunga et al). These authors consider this a sine qua non criterion for inclusion, and even if a patient with IgG > 5 g/L had every other diagnostic feature associated with CVID, they would not achieve a “probable” classification. We disagree and consider a standard based on local laboratory norms to be more appropriately inclusive when applied in conjunction with the other ICON criteria. Furthermore, it is irrelevant to state that “2.5% of the normal population

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would meet this criterion”³ because neither the ICON nor Ameratunga et al propose to use the IgG level as the sole determining factor.

Another important point is the inclusion (ICON) or exclusion (Ameratunga et al) of “asymptomatic” patients. Why should a diagnosis of CVID not be conferred on an asymptomatic patient who meets all of the other criteria proposed either by the ICON or Ameratunga et al? Furthermore, what constitutes an “asymptomatic” patient? What is the frequency, severity, or chronicity of infections that cross the threshold of a clinical manifestation of CVID? Must a patient bleed from thrombocytopenia, require transfusion for anemia, etc.? Perhaps they could be classified as “possible” CVID according to Ameratunga et al. However, we do not feel this single clinical feature affords a useful distinction in light of the immunologic abnormalities evidenced in all of the other criteria.

The ICON criteria place greater emphasis on establishing inadequate vaccine responses for the diagnosis of CVID. We agree with Ameratunga et al that this is not absolutely clear-cut for some patients.³ However, if this requirement is eliminated, regardless of whether or not patients are symptomatic, then one is much more likely to include the normal 2.5 % of the population with IgG < 2 SD below the mean. Furthermore, it then becomes questionable to include other criteria such as B-cell subpopulations in the definition, because those findings were established in cohorts of patients who had already been selected for having impaired vaccine responses, and Ameratunga et al acknowledge that these findings are not specific to CVID. Ameratunga et al also state: “patients with CVID who have had their primary vaccination series before antibody failure may be able to mount a protective response from long-lived memory B cells.”³ We are not aware of any evidence supporting this assertion. Regarding specific issues raised related to the definition of abnormal vaccine response, we stand by our statements in the ICON document.¹

Ameratunga et al include a low IgG3 level as one of the secondary laboratory criteria that can (in conjunction with at least 2 other elements from that list) support a diagnosis of CVID. We do not recognize any diagnostic utility of a low IgG3 level in a symptomatic patient with IgG < 5 g/L as proposed by Ameratunga et al. In that situation, at least 1 IgG subclass must be decreased and data showing that IgG3 subclass deficiency is more specific for CVID are lacking.

The histopathological findings mentioned by Ameratunga et al^{2,3} certainly can be found in patients with CVID. Again, and as acknowledged by Ameratunga et al, they are not pathognomonic for CVID and they have been described most consistently in patients selected for hypogammaglobulinemia and impaired vaccine responses. In addition, this type of information will not exist for many patients.

The utility of establishing “probable” versus “possible” classifications is debatable. The most important consideration is the consequence of placing an individual patient in one category or another. If the focus of the classification is a research question, then it could be useful to establish similarities and differences in the groups and possibly lead to better diagnostic criteria, or better understanding of the natural history of the disease. On the other hand, application of such classifications in a therapeutic context is more problematic. Yes,

most clinicians and third party payers recognize CVID as an indication for IgG replacement. However, not having CVID clearly does not exclude one from receiving IgG. There are a multitude of patients with immunodeficiencies having a component of antibody deficiency that are not CVID but which are, nevertheless, candidates for IgG replacement. Ameratunga et al say as much in their letter³ and it is unnecessary to invoke “unintended consequences.” Also, what is the therapeutic distinction between possible and probable CVID? Is probable CVID an indication for replacement, whereas possible CVID is not? Are both an indication for therapy? If so, then perhaps there is no therapeutically important distinction between them? In any case, we do agree with Ameratunga et al that clinical judgment is essential.

We formulated our criteria based on our review of evidence and literature derived from several large cohorts and registries around the world.¹ It might be an interesting exercise to apply these different sets of criteria in a prospective study to see precisely what the consequences are. On the other hand, in a few years, much of this discussion may become moot because of advances in our understanding of the etiology of CVID. Until then, we offer the ICON statements as our minimal set of appropriately inclusive and exclusive evidence-based criteria that will apply to the great majority of patients.

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References

1. Bonilla FA, Barlan I, Chapel H, Costa-Carvalho BT, Cunningham-Rundles C, de la Morena MT, et al. International consensus document (ICON): common variable immunodeficiency disorders. *J Allergy Clin Immunol Pract.* 2016; 4:38–59. [PubMed: 26563668]
2. Ameratunga R, Woon ST, Gillis D, Koopmans W, Steele R. New diagnostic criteria for common variable immune deficiency (CVID), which may assist with decisions to treat with intravenous or subcutaneous immunoglobulin. *Clin Exp Immunol.* 2013; 174:203–11. [PubMed: 23859429]
3. Ameratunga R, Gillis D, Steele R. Diagnostic criteria for common variable immunodeficiency disorders. *J Allergy Clin Immunol Pract.* 2016; 4:1017–8. [PubMed: 27587325]