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Editorial Comment

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A Haematologist's Guide to Coronavirus Disease 2019: Encyclopaedia or Doorstop?

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In this issue of *Acta Haematologica* Cheung et al. [1] review what they term a haematologist's perspective on the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic and on coronavirus disease 2019 (COVID-19). Their work is encyclopaedic with 128 references covering diverse haematological parameters including lymphocytes, T- and B-cell subsets, platelets, haemoglobin and coagulation parameters. They present data on hospital admission values and/or risk of death from COVID-19. They also discuss the impact of the SARS-CoV-2 pandemic on the blood product supply and on therapy of haematological cancers. Finally they discuss consensus guidelines from several societies.

Their review is timely. But is it a useful guide or a doorstop? Both. Readers will be able to quickly access relevant publications on these topics from the tables and references. On the downside there is little critical discussion or synthesis. For example, how common is lymphopenia and is it an accurate prognostic covariate? In Table 1 the authors list 26 studies including by my colleagues and me. Incidence rates of lymphocytopenia on hospital admission range from 26 to 83% (the text incorrectly says 26–80%). The problem is sample sizes range from 28 to 5,700 subjects. Should we give equal weight to all studies in the table? Probably not. Fifteen of the 26 studies have <100 subjects each, whereas 2 studies each have >1,000 subjects and 1 study 5,700 subjects, more subjects than the 20 others combined. Normally, authors provide a statistical analysis of this type of heterogeneous data, such as a weighted mean or median and confidence interval or interquartile range (IQR) followed by their conclusion. So, at the end of the day the reader is left wondering what the true incidence of lymphopenia on hospital admission is. My money is on results of the study of 5,700 subjects with a median of 63% (IQR 52, 75%), so about one-half of people. This lack of critical analyses of heterogeneous data is true of the other endpoints studied. Is this a killer? No, but critical statistical analyses would have been welcome. The issue of lymphocytopenia is especially important because it may correlate with survival. In a study of 1,571 subjects with COVID-19 we found a significant difference between 1,440 survivors (median 1.2 × 10E+9/L [IQR 0.9, 1.7 × 10E+9/L]) and 131 subjects who died (0.5 × 10E+9/L [0.4, 0.8 × 10E+9/L]; $p < 0.001$) [2]. Another example are data on admission prothrombin time. In the 8 studies cited in Table 1, values range from 12.4 s in a study of 94 subjects to 13.4 s in a study of 1,099 subjects. Again, this is important. In another study my colleagues and I found that a prothrombin time >12 s was also correlated with risk of death [3]. These and other data are summarized in a perspective in *Acta Haematologica* [4].

Another gift of the authors are Tables 2–4 of consensus management or therapy recommendations and guidelines from scientific or professional organizations such as

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the International Society of Thrombosis and Haemostasis, American Society of Hematology (ASH), European Hematology Association (EHA) and International Myeloma. What the authors fail to warn us of is that although these guidelines and recommendations seem sensible, none are evidence based. Readers will recall many things in medicine which seemed to make sense but were later proved wrong or even harmful. For example, it made sense to think gastric ulcers are caused by stress, but unfortunately in stepped *Helicobacter pylori* and a Nobel prize for rejecting seeming common sense. People estimate one-half of what we teach in medical school is wrong. The problem is we don't know which half. Other famous medical reversals include radical mastectomy for breast cancer, intracerebral stents for transient ischaemic attacks, coronary artery stents for stable angina and vertebroplasty. In haematology readers will recall misguided opinions regarding autotransplants for advanced breast cancer. For those who think medical reversals are uncommon I recommend *Ending Medical Reversal: Improving Outcomes, Saving Lives* by Prasad and Cifu [5]. In one analysis of 363 medical procedures published as effective in *The New England Journal of Medicine* 2001–2010, 40% were later proved ineffective or harmful and it was impossible to confirm the benefit of a further 20% [5]. In another study of 3,000 medical interventions considered standard of care in *The BMJ*, 65% were determined to be unproved, ineffective or harmful [6]. So much for seeming common-sense recommendations that are not evidence based. Montaigne summed it up nicely: "Nothing is so firmly believed as that which man knoweth least."

Lest I be accused of publication bias, might I direct readers to an experiment where I fed large numbers of genetically identical mice shredded SARS-CoV-2- or COVID-19-related consensus guidelines or sheets of blank paper with their laboratory chow for 1 week. I then let them attack a round of Stilton cheese onto which I had written "kill COVID-19" [7]. There was no difference in cheese consumption between the cohorts. So much for consensus guidelines, at least for mice. As Abba Eban noted: "Consensus means that lots of people say collectively what nobody believes individually."

Back to the article by Cheung et al. [1]. As I indicated, it is a useful reference document, but the reader will have to come to his/her conclusions about what the data mean. As for consensus recommendations: *caveat emptor*.

Conflict of Interest Statement

R.P.G. is a consultant to: BeiGene Ltd., Kite Pharma Inc., Fusion Pharma LLC, LaJolla NanoMedical Inc., Mingsight Parmaceuticals Inc. and CStone Pharmaceuticals; advisor: Antegene Biotech LLC; medical director: FFF Enterprises Inc.; partner: Neopharm Ltd, AZACA Inc.; Board of Directors: RakFond Foundation for Cancer Research Support; Scientific Advisory Board: StemRad Ltd.

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References

1 Cheung CKM, Law MF, Lui GCY, Wong SH, Wong RSM. Coronavirus disease 2019 (COVID-19): a haematologist's perspective. Acta Haematol. DOI: 10.1159/000510178.

2 Li Q, Cao Y, Chen L, Wu D, Yu J, Wang H, et al. Hematological features of persons with COVID-19. Leukemia. 2020 Aug;34(8):2163–72.

3 Xu J, Wang W, Ye H, Pang W, Pang P, Tang M, et al. A predictive score for progression of COVID-19 in hospitalized persons: a cohort study. Aging Death. 2020 [In press].

4 Gale RP. Perspective: SARS-CoV-2, COVID-19 and haematologists. Acta Haematol. DOI: 10.1159/000508021.

5 Prasad VK, Cifu AS. Ending medical reversal: improving outcomes, saving lives. Baltimore (Maryland): Johns Hopkins Press Health Books; 2015.

6 Polmear A. Clinical evidence. London: BMJ Publishing Group–Philadelphia: American College of Physicians/American Society Internal Medicine; 2000.

7 Gale RP. Can a disease be conquered by extensive publications, reading guidelines and interminable meetings? Leukemia. 2020 Aug; 34(8):1977–8.