Letters to the editor

Ebola, selective memory and educational costs

We now are a couple of voting cycles away from the 2014–16 Ebola virus disease epidemic in West Africa that claimed more than 10,000 lives, afflicted tens of thousands more, and struck economies and health support across West Africa. We have reached the apparent end of our third outbreak in the Democratic Republic of Congo since 2014 and another has just started, and have had a Marburg disease outbreak in Uganda in the mix. One would hope that we are learning from experience. However, we do not seem to be doing so well and have a large impediment in our way.

We have selective memories. We elevate in our thoughts that which has been important to us and our purpose, and we sometimes diminish that which is unpleasant or distracting. This becomes amplified in how we write. We have few words available to us in interviews, press releases and medical literature, and so focus on the elevated thoughts, paying short shrift to limitations, doubts and consequences. This has direct costs on how we educate health professionals. Medical school and other curricula focus increasingly on targeted references that index a reduced list of core ideas. Time spent exploring singular issues in depth in a lecture hall has been shunted to experiential settings attending to the clinical case at hand. On medical wards, recognition that even students and trainees must sleep coupled with real healthcare system finance burdens has translated into very focused faculty–student interactions. When, then, are important issues of professional practice discussed in depth? What permission have we as educators given to students, and as professionals given to peers, to incorporate lessons roundly with adult discourse? And, in this environment, how do we create and develop peers who tackle large, complex problems?

In this context, consider what a medical student would learn by engaging the literature on filovirus disease from the West Africa epidemic and subsequent events.

She would see that the disease was severe and had consequences for survivors.[1–4] She would note that favourable literature on some medical countermeasures against Ebola virus disease exist: diagnostics, vaccines and therapies.[5–11] She would see a clinical guideline and other practical guidance for patient care in resource-limited settings.[12,13]

However, the student would have trouble discerning that the clinical practice encouraged by those guidelines was sporadically in play during the epidemic, even in trial settings, making what to do with the product trials confusing. She would not know that case line lists on the ground well into the epidemic were notoriously variable and often of poor quality, forcing the loud narratives in the late summer and autumn of 2014 about the behaviour of the outbreak and the disease to rely upon the hope that data quality results from data volume. If she did recognise this, she might be persuaded that the problem was all about laboratory availability. She would note issues of stigma for patients and communities.[14] However, she would not see the systems-based stigmas that caused delay and consternation in mitigating the epidemic: the late incorporation of clinical needs in response actions; structural defects in the way that clinical practice and public health action intersect; the funny way funding mechanisms cause artificial divides in the conduct of research, risk management and biosecurity, that one can pay for a piece of laboratory equipment but not how the laboratory equipment gets its samples or is put to use through the safe and effective management of a patient; the awkward domestic and international interagency dialogues where every agency had and continues to have fits and starts about how to engage responses or make use of their fellow agencies in constructive vs competitive ways; and many others.

We have tools at hand to be better educators and peers on this aspect of professional development. We can insist as editors and peer reviewers for true incorporation and elaboration of opposing views and limitations. We can assess our learning objectives in at least a sampling of our curricula for use of implications from and lessons for health policy and operational practice. Perhaps most importantly, we can fight the rapid use of quickly available references by inculcating the habit of reading carefully what is found, searching for what is not said and seeking an opposite view. Hopefully, with the health emergencies that are sure to happen in the future, we will do better.

Declaration of interests

The author reports no conflicts of interest. The contents of this publication are the sole responsibility of the author and do not necessarily reflect the views, assertions, opinions or policies of the Uniformed Services University or the Department of Defense. Mention of trade names, commercial products, or organizations does not imply endorsement by the US Government. The author is an employee of the US Government and as such under the provisions of 17 U.S.C. 105, copyright protection is not available for this work.

DM Brett-Major
Department of Preventive Medicine and Biostatistics, F. Edward Hébert School of Medicine, Uniformed Services University, Bethesda, MD, USA

Email: david.brett-major@usuhs.edu

References

1 Jagadesh S, Sevalie S, Fatoma R et al. Disability among Ebola survivors and their close contacts in Sierra Leone: a retrospective case-controlled cohort study. *Clin Infect Dis* 2018; 66: 131–3.

2 Bah EI, Lamah MC, Fletcher T et al. Clinical presentation of patients with Ebola virus disease in Conakry, Guinea. *N Engl J Med* 2015; 372: 40–7.
3 Brett-Major DM. Thinking about Ebola. *J R Coll Physicians Edinb* 2015; 45: 15–7.
4 Dye C, Team WHOER. Ebola virus disease in West Africa–the first 9 months. *N Engl J Med* 2015; 372: 189.
5 De Santis O, Audran R, Pothin E et al. Safety and immunogenicity of a chimpanzee adenovirus-vectored Ebola vaccine in healthy adults: a randomised, double-blind, placebo-controlled, dose-finding, phase 1/2a study. *Lancet Infect Dis* 2016; 16: 311–20.
6 FIND WHO. *Joint WHO/FIND meeting on Diagnostics and Ebola Control*. Geneva. 12 December 2014.
7 Group PIW, Multi-National PIIST, Davey RT Jr et al. A randomized, controlled trial of ZMapp for Ebola virus infection. *N Engl J Med* 2016; 375: 1448–56.
8 Henao-Restrepo AM, Longini IM, Egger M et al. Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial. *Lancet* 2015; 386: 857–66.
9 Kennedy SB, Bolay F, Kieh M et al. Phase 2 placebo-controlled trial of two vaccines to prevent Ebola in Liberia. *N Engl J Med* 2017; 377: 1438–47.
10 OraSure Technologies I. Fact Sheet for Ebola Response Teams: Interpreting Results from the OraQuick® Ebola Rapid Antigen Test for use with Cadaveric Oral Fluid. 2016.
11 Siegel D, Hui HC, Doerffler E et al. Discovery and synthesis of a phosphoramidate prodrug of a pyrrolo[2,1-f][triazin-4-amino] adenine C-nucleoside (GS-5734) for the treatment of Ebola and emerging viruses. *J Med Chem* 2017; 60: 1648–61.
12 Lamontagne F, Fowler RA, Adhikari NK et al. Evidence-based guidelines for supportive care of patients with Ebola virus disease. *Lancet* 2018; 391: 700–8.
13 Brett-Major DM, Jacob ST, Jacquerioz FA et al. Being ready to treat Ebola virus disease patients. *Am J Trop Med Hyg* 2015; 92: 233–7.
14 Nuriddin A, Jalloh MF, Meyer E et al. Trust, fear, stigma and disruptions: community perceptions and experiences during periods of low but ongoing transmission of Ebola virus disease in Sierra Leone, 2015. *BMJ Glob Health* 2018; 3: e000410.

More on IgG4-related pulmonary disease

Owing to the fact that long-term complications of IgG4-related thoracic aortitis include aortic regurgitation, aortic aneurysm and aortic dissection,[1,2] patients such as the one recently reported with cough attributable to IgG4-related disease (IgG4-RD) complicated by thoracic aortitis[3] ought to have life-long monitoring for new-onset thoracic aortic regurgitation and aortic aneurysm, so that pre-emptive surgical repair can be undertaken where necessary.[1]

When pulmonary disease is complicated by cavitation during the course of IgG4-RD[3] there is potential for a misdiagnosis of pulmonary tuberculosis to be made, especially because pulmonary tuberculosis can, itself, coexist with IgG4-related lung parenchymal disease.[4] In a case report[4] a 68-year-old male had a history of cough, weight loss and fatigue. Chest CT showed left lung apical masses. Histology obtained after wedge resection of one of the pulmonary masses showed a whorled fibrotic pattern and a high concentration of IgG4-positive plasma cells (up to 100 per high power field). Furthermore, *Mycobacterium tuberculosis* was isolated from tissue culture. He improved after antituberculous chemotherapy, despite not receiving concurrent corticosteroid treatment for coexisting IgG4-RD. The authors of the case report[4] cited other cases in the medical literature that described the association of tuberculosis and IgG4-RD. They postulated that *M. tuberculosis* might activate an immunological chain reaction that culminates in the development of IgG4-RD. Finally, culture-positive tuberculous pleural effusion can develop during corticosteroid treatment of interstitial pneumonitis attributable to IgG4-RD.[5]

OMP Jolobe
Manchester Medical Society, Manchester, UK
Email: oscarjolobe@yahoo.co.uk

References

1 Stone JH, Khosroshahi A, Deshpande V et al. IgG4-related systemic disease accounts for a significant proportion of thoracic lymphoplasmacytic aortitis cases. *Arthritis Care Res (Hoboken)* 2010; 62: 316–22.
2 Uchida T, Hamasaki A, Kuroda Y et al. Immunoglobulin G subclass 4-related lymphoplasmacytic thoracic aortitis in a patient with acute type A aortic dissection. *Ann Thorac Cardiovasc Surg* 2017; [Epub ahead of print].
3 Slim D, Gunawardena H, Calvert JM et al. Ig G4-related pulmonary disease: protean impersonator. *J R Coll Physicians Edinb* 2018; 48: 130–3.
4 Bajema KL, Daniel JC, Hussain S et al. IgG4-related pulmonary and salivary disease associated with pulmonary tuberculosis. *Ann Am Thorac Soc* 2014; 11: 1165–7.
5 Suzuki N, Saeki T, Shimaoka Y et al. Two cases of IgG4-related disease with pleural effusion. [Japanese]. *Nihon Kokyuki Gakkai Zasshi* 2011; 49: 97–102.

Author's reply

Many thanks for your interest in our paper and important points. Just to clarify, in our case series[1] the patient with aortitis indeed remains under careful clinical follow up and monitoring, especially with regard to the aortitis itself and possible aortic regurgitation. The patient with the cavitating nodule had a negative tuberculosis screen but the potential co-existence with tuberculosis is interesting and needs further study. Since our case series, we have had a further two patients with confirmed IgG4-related disease (IgG4-RD) but with isolated non-cavitating nodules this time, which were resected with positive IgG4 staining. It is therefore important for those working in lung cancer clinics and multidisciplinary teams to be aware of IgG4-RD presenting as an isolated pulmonary nodule, which may or may not cavitate.

In addition to the potential management problems you have mentioned in pleural disease, another challenge can be in differentiating culture-negative tuberculous lymphocytic pleuritis without classical histology[2] from IgG4-RD lymphocytic pleuritis.[3]

ARL Medford
North Bristol Lung Centre, Southmead Hospital, Bristol, UK
Email: andrew.medford@nbt.nhs.uk

References

1 Slim D, Gunawardena H, Calvert JM et al. IgG4-related pulmonary disease: the protean impersonator? *J R Coll Physicians Edinb* 2018; 48: 130–3.
2 Valdes L, Alvarez D, San Jose E et al. Tuberculous pleurisy: a study of 254 patients. *Arch Intern Med* 1998; 158: 2017–21.
3 Medford ARL. Recurrent pleuritis: consider IgG4-related systemic disease. *Respiration* 2018; 85: 265.

Treatable alternative causes of extreme hyperferritinaemia

Although anaplastic large cell lymphoma proved to be the final diagnosis in the febrile patient with severe hyperferritinaemia and new-onset pleuritic pain,[1] the differential diagnosis should include more eminently treatable disorders such as adult-onset Still's disease (AOSD)[2,3] and disseminated tuberculosis.[4]

AOSD proved to be the eventual diagnosis in a 52-year-old male who presented with fever, neutrophil leucocytosis, and a previous history of pericarditis and pleuritic pain. His serum ferritin was 75,000 μg/l. After treatment with prednisolone he experienced rapid clinical improvement, accompanied by a progressive fall in serum ferritin.[2] Accordingly, there should be a high index of suspicion for AOSD in the presence of fever, neutrophil leucocytosis and hyperferritinaemia. Haemophagocytosis may also occur in AOSD.[3] Major criteria for AOSD include: fever, arthralgia, nonpruritic pink macular rash typically during febrile episodes, and neutrophil leucocytosis.[2]

Disseminated tuberculosis can also present with fever, neutrophil leucocytosis, hyperferritinaemia (serum ferritin 60,587 μg/l) and haemoghagocytosis.[4] In the case report of a 40-year-old female an additional finding was the presence of choroid tubercles in both fundi, notwithstanding the absence of miliary shadowing on chest radiography.[4] She experienced rapid clinical improvement after antituberculous chemotherapy and corticosteroids, and the choroid tubercles disappeared.[4]

In the presence of fever, neutrophil leucocytosis, hyperferrtitinaemia and haemophagocytosis the differential diagnosis should include AOSD and disseminated tuberculosis. Fundoscopy and mycobacterial blood culture should be part of the screening strategy.

OMP Jolobe
Manchester Medical Society, Manchester, UK
Email: oscarjolobe@yahoo.co.uk

References

1 Fretwell TB, Hanna M. An incidental finding of severe hyperferritinaemia: a lesson to be learned. *J R Coll Physicians Edinb* 2018; 48: 30–2.
2 Meijvis SCA, Endeman H, Geera ABM et al. Extremely high serum ferritin levels as diagnostic tool in adult onset Still's disease. *Neth J Med* 2007; 65: 212–4.
3 Arlet J-B, Le Thi Huong D, Marinho A et al. Reactive haemophagocytic syndrome in adult-onset Still's disease: a report of six patients and a review of the literatyre. *Ann Rheum Dis* 2006; 65: 1596–601.
4 Rathnayake PVTM, Kularathne WKS, De Silva GCV et al. Disseminated tuberculosis presenting as hemophagocytic lymphohistiocytosis in an immunocompetent adult patient: a case report. *J Med Case Rep* 2015; 9: 294.