Letters to the editor

Managing the COVID-19 pandemic: innovations, adaptations and leadership

The COVID-19 pandemic in the United Kingdom forced hospital teams to work under severe constraints on workforce, personal protection equipment (PPE), intensive care beds and ventilators. Individual hospitals had to come up with new organisational plans to manage the expected high numbers of patients over the following 12 weeks. We report our experience of preparing for the epidemic, workforce planning, and training junior doctors and nurses in the management of COVID-19 patients at Darlington Memorial Hospital in County Durham. This involved developing a risk stratification ward-round assessment proforma, rational allocation of PPE according to RAG (Red, Amber, Green) rating of wards based on the World Health Organization definition of aerosol-generating procedures (AGPs), building a brand new Acute Respiratory Unit (ARU) for continuous positive airway pressure (CPAP) ventilation and developing a multidisciplinary (MDT) pathway for invasive ventilation and palliative care.

In preparation for admission of COVID-19 patients, we initiated a Command Control Centre meeting each morning to plan staffing of all wards, allocate trainees and review any shortfalls. A consultants' WhatsApp® group was the portal for communicating between teams for clinical and non-clinical issues. This enabled us to deal efficiently with staff sickness shortfalls, arranging cover at short notice, as well as sharing clinical updates, publications and good practice guidelines. A new 8-bed stream of Respiratory Emergency Care was created in the Accident and Emergency Unit (called the Respiratory ED), manned 24/7 by a specialist trainee and consultant physician, triaging patients coming to the hospital, with access to portable radiology and on-site nasopharyngeal swab collection for SARS-CoV-2 RT-PCR testing. Two 30-bed wards were created on the Surgical Floor for COVID assessment and COVID-positive patients, with appropriate PPE and staffed by a consultant and 4–5 trainees, 8 am–5 pm, seven days a week. Our existing Acute Medical Unit (AMU) became a hybrid AMU with integrated same-day emergency care (SDEC) looking after unwell non-COVID patients during this period. Non COVID-19 patients were moved to three other wards on a separate floor to reduce hospital transmission of infection.

A COVID-19 risk stratification proforma (Appendix 1) was created for ward rounds, to identify the highest risk patients who might need respiratory support and invasive ventilation. An ICU suitability assessment was done by our ICU team and decisions ratified at an afternoon MDT meeting. Patients who had a SpO2 < 93% and a SpO2/FiO2 ratio of <315mm Hg were considered for non-invasive or invasive ventilation. Patients who had a Clinical Frailty Scale of >5 according to the NICE Critical Illness Algorithm were referred to Palliative Support team.

To further reduce the risk of hospital-related transmission, visiting by family members was completely stopped during this period, but digital technologies such as smartphone video calls and iPad video meetings were introduced. An off-site community hospital was expanded to provide intermediate care to step down patients from the acute site for rehabilitation. The Royal College of Physician SPACES (Sharing Patient Assessments Cuts Exposure for Staff) approach was adopted on COVID wards and medical and nursing staff trained to use this model.

We also developed a database for COVID-19 to collect data on clinical epidemiology, respiratory and non-respiratory symptomatology, blood investigations including risk prediction using CRP, lymphocyte counts, platelet counts and SpO2/FiO2, radiology and ventilation need. Our initial figures between 15 March 2020 and 14 April 2020 showed a total of 399 positive RT-PCR test results in the geographical catchment area of County Durham, of which 268 were in non-admitted patients and 131 in admitted patients. Of this number 51 were admitted to our hospital. The overall hospital mortality for COVID-19 related admissions on 18 April 2020 in the County Durham was 104, which was 0.7% of the total national mortality of 13,918 deaths.

The second phase of our activity during the COVID-19 pandemic will involve a programme of recovery from the intense COVID-19-related inpatient activity to resumption of elective activity in all specialties. This will include restoring outpatient clinical activity as well as restarting diagnostic procedures such as endoscopy, bronchoscopy and cardiac physiology.

In summary, our experience shows that it is essential to plan every aspect of hospital management during a pandemic well in advance, from dedicated areas for assessment and triage, protocols for escalation and palliative care, non-invasive and invasive ventilation, to staffing and PPE in order to manage the needs of the community and not be overwhelmed by the rapid increase in numbers of patients admitted to the hospital. This strategy also keeps mortality at the lowest possible level, with a clear understanding that the elderly and frail patients will die from COVID-19 disease, but they will be looked after with dignity in their last moments.

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Diagnosis of tuberculosis with molecular methods and treatment of Axial skeleton Tuberculosis

The recent article by Rohan et al in this journal described an interesting case of axial skeleton tuberculosis (TB) mimicking malignancy in a health care worker (HCW) in India.[1] The diagnosis was made by polymerase chain reaction (PCR), a molecular diagnostic method from the pus. India has the second largest burden of multidrug resistant TB (MDR-TB), defined as resistance to isoniazid and rifampicin, in the world.[2] WHO estimates that India has 2.8% MDR/Rifampicin resistance amongst newly diagnosed tuberculosis cases and 12% amongst previously treated cases.[3] Considering that the patient was a health care worker, there was a high probability that they were infected at work and could have acquired drug resistant tuberculosis as an occupational hazard. It would have been pertinent to know if the diagnosis was based on a nucleic acid amplification test (NAAT) e.g. Xpert MTB/RIF, as such a test can detect Rifampicin resistance as well and much earlier than the culture results become available.[4]

Rifampicin resistance is also used as a surrogate marker for MDR-TB by WHO, as at least, 90% of all Rifampicin-resistant clinical isolates are resistant to Isoniazid.[2] The results of the final TB culture and drug susceptibilities were also not described. In this particular case of skeletal TB diagnosed in a HCW, knowing if the TB was resistant to Rifampicin or not prior to starting treatment would have had many treatment implications; as literature on drug regimen and duration of treatment for resistant TB is limited and some reports of treatment duration of up to 24 months have been described.[5] It was heartening to know that the patient did well, but we feel the above issues should be considered before diagnosing and treating tuberculosis.

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Authors' reply

We would like to thank Kelly et al. for providing valuable comments on our paper. As rightly pointed-out, India has a high burden of multi-drug resistant tuberculosis. Health-care providers are at constant risk, given the level of exposure.[1] The woman described in our paper was a gynaecologist practising in India, who was diagnosed with multi-focal tuberculosis of axial skeleton.[2] Histopathological examination of the paravertebral collection revealed granulomatous inflammation and necrosis, which raised the suspicion of tuberculosis. The diagnosis of tuberculosis was established on the basis of nucleic acid amplification test obtained on pus aspirated from paravertebral collection, which did not reveal resistance to rifampicin.[3] Therefore, the patient was treated with a combination of rifampicin, isoniazid, ethambutol and pyrazinamide for the initial two months followed by rifampicin, isoniazid and ethambutol.

Nucleic acid amplification tests have enabled early diagnosis of tuberculosis.[4] In addition, they have a high positive predictive value.[5] However, they detect deoxyribonucleic acid both from dead and live organisms.[6] In addition, previous Bacillus Calmette–Guérin vaccination can also give rise to a positive result.[7] Therefore, we agree that the results of the final culture and drug sensitivities should have been mentioned in the manuscript. The results of culture received six weeks after the diagnosis, revealed growth of mycobacterium tuberculosis, sensitive to all the first-line anti-tubercular drugs. The patient responded remarkably to treatment and continues to be afebrile with no musculoskeletal complaints; acute phase reactants are normal.

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The dichotomy between PubMed-listed journals and low-quality journals

After reading the analysis of predatory journals vs journals who publish articles listed in Pubmed,[1] I wish to express my mixed feelings on the subject.

Firstly, I have published several articles (including three reviews) which are listed in PubMed, and I have published three reviews in low quality journals not listed in PubMed. It is the issue of review articles that I specifically wish to address.

The following are the obstacles encountered by a prospective author who wishes to publish a review article in a PubMed listed journal:

- Some journals openly state that unsolicited review articles are unwelcome. They prefer to solicit review articles from opinion leaders with established reputations.
- Others specify a word count limit and reference list limit, regardless of the complexity of the subject.
- Some editors will reject a review article out of hand, without even submitting it for peer review. Then, there is the triumph of form over substance. If the manuscript does not conform to the desired format (i.e. house-style), instead of coaxing the author to get the format right editors find it much easier to reject the article out of hand.

On the other hand, some predatory journals are more flexible. Their referees will rate the manuscript for originality, presentation, and other qualities, in a transparent manner which the author will understand. Thereafter, if there are issues regarding form rather than substance, the referee will coax the author in the right direction until a satisfactory compromise is reached between author and referee. That was my experience with *Atypical manifestations of pulmonary embolism*[2] which had been rejected by a number of PubMed-listed journals.

My latest offering was *Clinical characteristics in STEMI-like aortic dissection vs STEMI-like pulmonary embolism*,[3] also nurtured by a journal not listed in PubMed. It was nearly 10,000 words long with 229 references; definitely 'out of bounds' for many PubMed-listed journals.

My own view is that journals which are not PubMed listed should not accept research papers. The scientific community simply cannot accept lapses in scientific scrutiny which, arguably, are more likely to occur in the low quality arena; but review papers belong to a different category. In a review paper the 'raw' data are common knowledge, like 'primary sources' in world history. The reviewer merely offers his interpretation of the primary source material. And that is an honest but subjective dimension which should be open to debate. Within reasonable limits, a word limit is irrational, because the length of the text and the number of references surely depends on the complexity of the topic and also depends on the number of 'primary sources' required.

Finally, if the author has gone to considerable trouble to prepare the manuscript, the Editor should have the decency to submit it to peer review rather than reject it out of hand, without the benefit of that kind of scrutiny.

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Is there a clear division between predatory and low-quality journals and publishers?

In a recent editorial, Misra and Ravindran discussed the difficulties in differentiating scholarly from unscholarly journals, highlighting attempts by the International Committee of Medical Journal Editors and others in trying to differentiate the wheat from the chaff of publishing venues.[1]

They argued that the academic community is divided regarding the precise definition of what a 'predatory' journal or publisher is, despite years of the existence of this phenomenon, and that there also exists ambivalence among policy makers and leading scholars. This may be because many such borderline entities fall into a grey area of characterisation, displaying some predatory characteristics, but also some legitimate scholarly properties. Their discussion raises important points, but also makes the unfortunate error of equating a predatory journal with a low quality one, open access or not, as indicated by the conjunction 'or' in the title of their editorial. In many instances, predatory publishers are very obvious, such as OMICS,[2] but in other instances, a predatory entity is difficult or impossible, to distinguish from a low quality one because the characteristics that are employed may be exploitative, rather than predatory.[3]

The National Centre for Biotechnology Information's (NCBI) LitCovid indicates that over 77,000[4] papers related to COVID-19 have been published, yet scholars have yet to

examine how much of this health related literature has been published in predatory versus legitimate, indexed and peer reviewed venues, even though evidence already exists of unscholarly publishing practices related to COVID-19.[5] Academics, clinicians and public health officials around the world, under strain from the health, societal and psychological pressures imposed by this pandemic, have had little time to examine whether information that may be damaging to health has been published in predatory or unscholarly venues. This is a priority: only by using open science, data, and peer review policies can we ensure that publishing on COVID-19 is properly vetted, that the process is transparent, and that the outcomes are papers that benefit academia, society and humanity.

One way of attempting to differentiate legitimate scholarly, peer-reviewed journals from unscholarly predatory journals that do not undergo rigorous peer review is through the creation of whitelists and blacklists, such as those created by and curated by Cabell's International, the Directory of Open Access Journals (DOAJ), or even indexing platforms such as PubMed, Scopus or Web of Science, but such lists and indexes suffer from several limitations: type I and type II misclassification errors, in which a perfectly legitimate journal might be erroneously excluded or blacklisted, or a truly predatory journal might be erroneously included; a negative stigma attached with being blacklisted, and the potential for long-term, and sometimes irreversible, reputational damage.[6]

A very serious issue that few are addressing is whether peer reviewers who aided the publication of literature in predatory venues, or approved the publication of unscholarly work, are rewarded at the peer reviewer recognition site, Publons.[7] To fortify the scholarly, transparent and effective nature of peer review and to make scholarly publishing more accountable, the following behaviors should be classified as predatory: fake claims of peer review; excessively long desk rejections; failure to respond to author queries.

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Authors' reply

We thank Drs Jolobe and Teixeira da Silva for their interest in our editorial. We do not agree that rejecting without peer review (so called 'desk rejection') is in anyway an adverse reflection on a journal's editorial process. In fact, based on our long experience as the editors of several journals we would like to reassure them that while making such decisions a variety of factors are considered by the editor(s) and are never taken lightly.[1,2]

If anything, such decisions are quick and allow editors and reviewers to focus on good quality manuscripts suitable to a journal's scope. Furthermore, authors have to appreciate that a journal has the right and responsibilty to maintain the standards according to its collective editorial vision. It may justifiably have certain article categories as commissioned only, and have instructions to guide on the length of the manuscript and number of references etc according to its requirements. A poorly written manuscript runs the risk of a journal losing intrerest.[1,2] On the other hand, predatory or low quality journals have to be more accommodating in all these aspects. Therefore, it is essential for the authors to be aware of publishing practices of different journals.[3]

From the editor's perspective, creation of black or white lists or having only PubMed listed journals publish research papers is not a panacea to deal with predatory or low quality journals. One has to consider the fact that authors might be under undue pressure to get published and in this context such journals appear to offer an easier platform.[4] Broader questions remain as to whether the authors would be guided and informed by such reveiws or research papers (and by extension, be prepared to cite), if they know that it has been published previously in such a journal.[5]

Finally, while the scientific world coninues to debate on the finer charateristics of low quality and predatory journals, as implied in the title of our editorial, there is little doubt that the two have several common features which should alarm the authors and scientific community at large.

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The growing evidence for isolated anti-Ro52 antibodies and autoimmunity: A report of four cases

The presence of a positive antinuclear antibody (ANA) in significant titers, by itself, increases suspicion for a connective tissue disease (CTD), in the absence of clear cut features for the same. Also, an ANA profile (line immunoassay), evaluating the presence of multiple autoantibodies, may help in further characterization of the CTD, specially where there is a high index of suspicion, but the ANA is negative. In the past, the detection of isolated anti-Ro52 antibodies was traditionally considered clinically insignificant. Recent evidence implicating these antibodies with a variety of autoimmune manifestations constitutes a paradigm shift in understanding, and merits awareness and further investigation. The varied and atypical clinical presentations associated with isolated anti-Ro52 antibodies presents a diagnostic and therapeutic dilemma among physicians and rheumatologists. A negative antinuclear antibody (ANA) sometimes adds to the complexity of the issue. This brief report of four cases with isolated anti-Ro52 antibody positivity on line immunoassay exemplifies its association with various autoimmune manifestations requiring immunosuppression (Table 1).

Ro52 belongs to the TRIM (tripartite motif proteins) family of proteins and is structurally different from Ro60 protein.[1] Though it localizes to the cytoplasmic compartment of cell, it has the ability for nuclear translocation under pro-inflammatory conditions and modulates transcription via ubiquitination.[1] It thus downregulates the interferon-regulated genes and the pro-inflammatory cytokines. Anti-Ro52 antibodies, in association with other autoantibodies, are seen in a multitude of autoimmune disorders including Sjogren's syndrome, systemic lupus erythematosus (SLE), cutaneous lupus erythematosus, neonatal lupus erythematosus, systemic sclerosis, inflammatory myopathies, and autoimmune hepatitis.[2]

The presence of anti-Ro52 antibodies on line immunoassay in isolation were observed in these four patients, of which one had a negative ANA by indirect immunofluorescence (IF) method on HEp-2 cells. A diagnosis of Neuro-Sjogren's syndrome was made in one patient based on minor salivary gland biopsy with a focus score of two. This patient had predominant neurological manifestation without any other autoimmune features including the sicca symptoms. This highlights the importance of anti-Ro52 antibody for diagnosing Sjogren's syndrome. Two patients presented with interstitial lung disease (ILD) and subsequently were labelled as interstitial pneumonia with autoimmune features (IPAF) as per the European Respiratory Society/American Thoracic Society (ERS/ATS) criteria.[3] The other clinical characteristics of all these patients are shown in Table 1.

Table 1 Clinical features of isolated anti-Ro52 antibody positive patients (N=4)

Age (years)/ Sex	Final diagnosis	Clinical features	ANA (HEp-2) and other autoantibodies	Imaging and other findings	Treatment given
20/F	Neuro-Sjogren's syndrome	Binocular diplopia, paraparesis, paraesthesia, seizure	3+Fine speckled Aquaporin-4+	MRI brain: normal, spine: long segment transverse myelitis from cervico-medullary junction to C6; abnormal VEP (left); minor salivary gland biopsy: focus score 2	Pulse MPS, PDN (1mg/kg), CYC
40/M	IPAF	Fever, exertional dyspnea, proximal muscle weakness (Grade 4 power on MRC scale), Raynaud's phenomenon	3+Nuclear dots, cytoplasmic dense fine speckled	HRCT Thorax: NSIP, Mild PAH Normal muscle enzymes and MRI thigh EMG: proximal myopathy	PDN (1mg/kg) CYC
58/M	IPAF	Exertional dyspnea	3+Homogenous	HRCT Thorax: Fibrotic NSIP Moderate PAH	PDN (1mg/kg) CYC
30/F	UCTD Obstetric APS	Symmetrical polyarthritis, pregnancy loss (2 second trimester spontaneous abortions)	ANA Negative, Ig M anti-cardiolipin (persistent low titre)	Raised ESR and CRP	HCQ

M: Male; F: Female, IPAF: Interstitial pneumonia with autoimmune features; UCTD: Undifferentiated connective tissue disorder; APS: Antiphospholipid syndrome; MRC: Medical research council; ANA: Antinuclear antibody; VEP: Visual evoked potential; HRCT: High-resolution computed tomography; NSIP: Non-specific interstitial pneumonia; PAH: pulmonary arterial hypertension; EMG: Electromyography; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; MPS: Methylprednisolone; PDN: Prednisolone; CYC: Cyclophosphamide; HCQ: Hydroxychloroquin

A study by Singh et al reporting 38 patients with isolated anti-Ro52 antibodies merits attention in this context.[4] Autoimmune manifestations were seen in 55% of patients with pulmonary involvement being more common. Interestingly, ten patients (27%) had a negative ANA; and non-autoimmune conditions including malignancy were also reported. A retrospective analysis by Malik et al reported the association of anti-Ro52 antibodies in various autoimmune rheumatic diseases, in addition to the primary diagnosis of inflammatory arthritis in 12 patients.[2] They also observed that 10% of patients had a negative ANA and ENA, despite having features of connective tissue disease.

When classical clinical features suggestive of a CTD are associated with a positive ANA, the clinician has no problems in labelling the disease to be of autoimmune origin. However, in the presence of features atypical for a CTD or a relative paucity of clinical features suggesting a CTD or when associated with a negative ANA, the detection of anti-Ro52 antibodies exclusively on a line immunoassay should not be ignored. Increasing recognition of the above allows for a diagnosis of CTD and avoids delay in initiation of definitive therapy.

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Megaloblastic Anaemia

I read with interest the case report entitled "Microangiopathic haemolytic anaemia and thrombocytopenia due to combined vitamin B12 and folate deficiency masquerading as thrombotic thrombocytopenic purpura"[1] in the recent issue of the Journal. I believe that the title of the report has the potential to mislead the readers for the following reasons.

There is no evidence of thrombotic thrombocytopenic purpura (TTP) with a normal ADAMTS-13 and no recorded fever or renal impairment. The subdural haematoma might have been related to mild trauma in the presence of thrombocytopenia. The peripheral blood film shows oval macrocytosis, anisocytosis and a few fragmented red cells, changes more associated with megaloblastosis and not the classical picture of a microangiopathic haemolytic anaemia.

The relatively low MCV may be due to a concomitant iron deficiency or a thalassemic trait[2,3,4] Iron status of this patient is not mentioned. It is also not recorded when the patient last had chemotherapy for lymphoma, although this is of importance in relation to the haematological findings.

The raised reticulocyte count is against megaloblastosis but might have been due to previous haematinic therapy unknown to the attendants.

Severe vitamin B12 deficiency may be related to disease in the terminal ileum. The jejunal resection may have interfered with vitamin B12 binding sites and as this was 5 years previously, vitamin B12 stores may have been exhausted.

Therefore, the case seems clearly to be of severe megaloblastic anemia with a pancytopenia, ineffective erythropoiesis with an associated raised LDH, indirect bilirubinaemia and red cell changes in the blood.

The case illustrates some important good practice points:

- Severe megaloblastosis is an emergency and requires appropriate immediate medical treatment.
- It should be recognized by careful evaluation of a blood film and bone marrow aspirate.
- Severe megaloblastosis can cause a pancytopenia with a cellular marrow and ineffective haematopoiesis.
- Mild indirect hyperbilirubinaemia is evident in many cases and often associated with a markedly raised LDH. This should not initially cause us to look for other causes of haemolysis.
- The cause of the megaloblastosis should be ascertained which will usually be vitamin B12 or folate deficiency. The cause of the particular deficiency should be then investigated.
- Iron status should be ascertained initially. Untreated concomitant iron deficiency may lead to a failure of a full haematological recovery.

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