Guidance production before evidence generation for critical issues: the example of COVID-19

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Production of guidance in rapidly evolving areas where evidence is absent or fragile is challenging and needs to use rigorous methods interpreted with caution https://bit.ly/3jpChqk

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The coronavirus disease 2019 (COVID-19) pandemic has inflicted a considerable pressure on populations, healthcare systems and community organisations worldwide, due to the fast spread of the disease and its huge global burden of morbidity and mortality, healthcare resource consumption, and societal and economic implications [1].

Since its appearance in December 2019, it has become rapidly obvious that this new disease behaves very differently from previously known viral pneumonias in terms of risk factors, biological, radiological and clinical presentation, natural course and response to therapy [2], making specific research and clinical guidance mandatory to understand the disease, deliver appropriate care and support public health decisions.

Although the clinical picture is very heterogeneous, the potential for severe life-threatening conditions in adults comes from the respiratory component of the disease: airways, alveolar and vascular damage, inflammation, dysfunction and repair can lead to rapidly progressive acute hypoxemic respiratory failure [3]. As yet inexplicably, the manifestations of COVID-19 are very different in children and young people, with the respiratory illness usually being trivial, but a rare, severe Kawasaki-like vasculitic illness has been described [4]. Since respiratory failure is the main determinant of short-term prognosis in adults, it should be a top priority for research and development of clinical guidance. Underlying mechanisms include a

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"cytokine storm", mitochondrial dysfunction, DNA damage and oxidative stress [5]. Attempts to classify the pathological features of COVID-19-related respiratory disease in autopsy series have identified epithelial, fibrotic and vascular patterns [6]. The latter include endothelitis/vasculitis, thrombosis and angiogenesis [5]. The corresponding radiological abnormalities typically comprise multilobar ground-glass opacities and consolidations with posterior, inferior and peripheral predominance, associated with vascular thickening [7]. Considering these features of the disease, proposed pharmacological approaches have included not only molecules with antiviral properties but also anti-inflammatory agents (glucocorticoids, anti-cytokines) and anticoagulants [8]. Respiratory support strategies were initially limited to oxygen therapy and invasive mechanical ventilation, and subsequently high-flow nasal oxygen therapy, continuous positive airway pressure ventilation and non-invasive ventilation have been deployed [9]. These noninvasive approaches had raised concerns initially because of the risk of viral aerosolisation. However, subsequently, it became clear that if appropriate individual protective measures are implemented, the risk should be small. Numerous clinical studies have been undertaken to document the benefit/risk ratio of these various therapeutic resources. But despite this "explosion" of dedicated research, gathering the necessary evidence takes time and, in the meantime, clinicians and healthcare systems urgently required some interim guidance on how to treat patients and where to allocate resources.

Another major source of concern arising from the acute features of COVID-19 lung injury is the risk of long-term chronic respiratory sequelae, suggesting patients must be followed up after an apparent recovery from the acute phase, and testing non-pharmacologic (*i.e.* rehabilitation) and pharmacologic (*e.g.* to prevent lung fibrosis or slow its progression) therapeutic approaches [10]. As for treatment trials, many follow-up cohorts have been initiated. However, the evidence required to develop standards of care for follow-up will be available only when sufficient time has elapsed to obtain results from these initiatives. In the meantime, clinicians and public health deciders again need guidance on how to follow and provide support to these patients, and on how to make the required resources available.

This apparent contradiction between the lack of immediately available high-level evidence and the wish to have immediately available guidance poses a threat to guideline developers, leading some institutions to develop dedicated evidence-synthesis frameworks [11]. This is further complicated by the politicisation of the crisis, with political leaders trying to circumvent scientific evidence in favour of a "quick-fix" for short-term gain. The gold standard on which guidelines development should rely is a systematic review of the evidence, complemented by rigorous consideration of values, preferences and costs within an evidence-to-decision framework. This process has been formalised by the GRADE group and others [12]. But this approach has some limitations in circumstances such as the COVID-19 pandemic: one limitation is the lack of evidence, another is the time required to implement the process. One way of addressing the uncomfortable absence of strong scientific evidence and urgent need to guide professionals and patients is to gather empirical evidence. As for evidence-based guidelines, this process needs to be standardised, transparent and somehow systematic. Achieving this goal can take advantage of existing methods to reach consensus, including those based on the Delphi process initially developed by the RAND corporation [13]. More recently, such methods have been integrated in a process named CORE for Convergence of Opinion on Recommendations and Evidence, a terminology that was subsequently changed for Convergence of Opinion on Suggestions and Evidence, to highlight that it does not produce evidence-based recommendations [14]. Briefly, clinical questions are presented in a PICO-like format (Patient population targeted, Intervention of interest, Comparator(s), Outcomes). Multiple choices are proposed, corresponding to strong or weak agreement or disagreement with the proposition, or neutrality. A free text box is available for comments. For each question, the level of agreement between voters is calculated. Several rounds can be organised within a short timeframe. The underlying concept is that gathering votes and opinions from a large number of participants may result in propositions similar to what would be recommended following strictly evidence-based processes, since expert voters as a group know the literature and the evidence it provides, and have sufficient experience and expertise to put it in the right perspective. Accordingly, CORE was shown to produce suggestions that are highly concordant with those developed using Institute of Medicine-adherent methodology for clinical practice guidelines. However, its reliability has been debated [15–18]; indeed, the history of medicine is a graveyard of what once seemed good ideas at the time to experts. One important advantage of this method compared to clinical practice guidelines based on systematic reviews is the increased speed and lower cost of the process, making it appealing when rapid response is required, as with the COVID-19 situation. In addition, this methodology can help in areas that are difficult or complex to address with randomised controlled trials, *e.g.* palliative medicine, where CORE methods have been used to set principles, priorities and/or guide care [19]. Importantly, developers of CORE-based guidance outlined that CORE and GRADE should not be viewed as opposed but as complementary, with CORE having the potential to rapidly identify where systematic reviews are not mandatory (*i.e.* where a consensus is easily reached) and where they are (*i.e.* when no consensual suggestions can be made) [18]. By definition, however, the outputs of CORE and GRADE will

necessarily change when new evidence is accumulated; the best processes in the world will never second-guess the future.

Early on in the COVID-19 pandemic, Task Forces were convened by various scientific societies including the American Thoracic Society (ATS) and European Respiratory Society (ERS), with the aim to rapidly address the most important clinical questions on COVID-19 management, and produce consensus guidance on clinical care, healthcare organisation and research.

This issue of the *European Respiratory Review* (*ERR*) presents an updated guidance on COVID-19 management produced by an ATS/ERS coordinated Task Force using the CORE process [20]. The first six questions deal with in-hospital management and the Task Force suggests the use of remdesivir and dexamethasone but not hydroxycholoroquine (outside clinical trials) in patients requiring respiratory support (from nasal oxygen therapy to invasive mechanical ventilation). The next questions address post-hospital follow-up and referral for rehabilitation. Interestingly, this topic was also tackled in a previously published ERS/ATS coordinated Task Force using the same methodology [21]. For both Task Forces, the number of voters was above 90. Despite being released within a short period of time and using similar methods, some apparent discrepancies can be identified in these documents: the ATS/ERS coordinated taskforce on COVID-19 management published in this issue of the *ERR* could not make any recommendation on post-hospital respiratory follow-up and rehabilitation due to lack of consensus, while the ERS/ATS coordinated Task Force on rehabilitation suggested that "patients with COVID-19 should have a formal assessment of physical and emotional functioning at 6–8 weeks following discharge, to identify unmet rehabilitation needs" [21]. In addition, this Task Force suggested that "follow up of a hospitalised patient with COVID-19 should include measures of respiratory function and exercise-capacity at 6–8 weeks following hospital discharge" [21].

Such differences raise two groups of questions. The first group comprises very practical clinical questions: at the end, what should clinicians do and what are the resource implications? Should all patients be followed or only some specific subsets, and if so, for how long and at what intervals? Which investigations should be proposed? Should all patients or only specific subsets be referred for pulmonary rehabilitation? When should this occur? How should they be assessed? The second group of questions refers to the CORE methodology itself: is it that reliable? Are there situations in which it is more appropriate and robust? How should it be used to ensure consistent outputs? What should readers know to appropriately interpret and understand the propositions?

Several hypotheses can be discussed to explain the observed differences regarding guidance on post-hospital follow-up and rehabilitation of COVID-19 patients. Interestingly, many authors outlined that there is no real gold standard for consensus development [22]. First, the way questions and propositions of answers are formulated can influence the choices expressed by voters. In the ATS/ERS document, participants were asked whether they suggested routine pulmonary function testing, chest computed tomography, trans-thoracic echocardiography, and cardiopulmonary exercise testing to establish new baselines. The terms "routine" and "to establish a new baseline" were absent from the ERS/ATS document on post-COVID-19 rehabilitation, which could lead to differences in interpretation and, thus, answers. Similarly, the ATS/ERS document published in this issue of the *ERR* asked whether voters suggested routine referral for rehabilitation while the previously published ERS-ATS one asked whether subjects with a need for rehabilitative interventions should receive a comprehensive rehabilitation programme. It must be noted that such differences in formulations can be influenced by the composition of the initial core group that formulates the questions. It is impossible to formally determine their (likely) impact on final votes.

Secondly, the composition of the whole panel of voters certainly has some influence on the final output [23]. This is actually true for all types of Task Force including those using GRADE: it is always crucial to gather multidisciplinary panels representing all relevant stakeholders (especially patients), and to remember that no method is totally exempt from some subjectivity (for instance, in outcomes prioritisation and when working on the evidence-to-decision framework). In contexts such as COVID-19 (new, rapidly spreading and potentially lethal respiratory infectious disease with multisystem manifestations), developing guidance requires input primarily from respiratory and infectious disease physicians, as well as internists and intensivists. Some aspects may also benefit from input from various other medical specialties and from physiotherapists, nurses, patients, *etc*. The balance between these origins and between key opinion leaders with academic background and field practitioners is key to ensure balanced votes. However, it can also lead to difficulties in obtaining consensus, while selected experts highly specialised in a field would easily reach an agreement in this very field. Importantly, the ATS/ERS document on COVID-19 management underlines that, although voters felt that follow-up and, if needed, referral for rehabilitation were potentially useful, many were reluctant to recommend them routinely to avoid overwhelming healthcare systems [20]. Thus, they balanced medical needs with the need to rationalise resource use and preserve equity; in other words, they took feasibility and ethical issues into

consideration rather than relying only on the potential clinical utility of the interventions of interest. This again highlights the potential influence of voters' characteristics, formulation of propositions and instructions on what should guide votes.

Finally, the level of available evidence certainly influences the results of CORE processes: the stronger the evidence (provided it is convergent), the more likely it is to reach a consensus; in addition, the feedback provided to participants between rounds, which is influenced by the evidence and how it is perceived, can have an impact of further votes [22]. Consequently, as already suggested, difficulties in reaching a consensus are important and mandate further research, and/or systematic reviews where evidence has already been produced. In the COVID-19 domain, follow-up cohorts and studies on rehabilitation will certainly provide important data to inform future guidance. No matter how expert a panel, if there is no evidence there can be no evidence-based proposals. We do not know what 1 year post-COVID-19 clinical data will look like, so it is mandatory to find out and modify recommendations accordingly.

It is obviously crucial that CORE processes are as transparent as GRADE-based recommendations: rules guiding the selection of the core group in charge of the coordination and formulation of questions, and of the whole panel need to be made available, as well as the detailed characteristics of their members. Conflicts of interest need to be disclosed and appropriately managed. Percentages of respondents and their characteristics compared to those of the whole panel can also be of interest. As appropriately done in the recent CORE-based guidance coordinated by ATS/ERS or ERS [19–21], propositions or lack thereof need to be explained using panellists' comments and cited references. But one recurrent difficulty with guidelines documents is that many readers focus exclusively on the guidelines themselves without reading the discussion. Thus, when important considerations arise from the discussion, they need to be vigorously highlighted by authors. As mentioned above, a good example is the discussion on follow-up in the ATS/ERS document: "There was agreement among the Task Force that it would be useful to have pulmonary (PFTs and chest CT scans) and cardiac (TTE and CPET) measurements within 30–60 days after discharge to assess the severity of impairment and to establish a baseline from which to follow recovery over time. However, there was also concern about the practicality of obtaining these tests during the ongoing COVID-19 pandemic." [20]. The lack of final suggestion on this topic in the document should not lead us to consider follow-up as unnecessary.

Finally, the quality of available evidence always needs to be questioned. The COVID-19 pandemic has also brought with it significant challenges to data interpretation and quality which may impact on guidelines and recommendations. For good and understandable reasons, there is pressure to get data into the public domain rapidly, to improve patient care. But there are inevitable significant conflicts of interest, and temptations to cut corners. Investigators want the academic kudos of being first in the queue. Papers are being made available on the web on pre-review sites. Peer review has an important purpose and is irreplaceable; a manuscript which has not been peer-reviewed cannot be given the weight accorded to one which has. Journal editors are keen to publish potentially highly cited papers and increase the journal impact factor. Under the cloak of good intentions to get information into the public domain, perhaps peer review standards may have dropped, or reviews been over-hasty. The combination of these author and journal factors may have contributed to the withdrawal of a significant number of COVID manuscripts in which intrinsic weaknesses or biases went initially unnoticed due to lack of editorial scrutiny. Notably also, there is increasing political pressure to pressure regulators to license medications for which there are inadequate data, an obvious example being the fast tracking of hydroxychloroquine and its subsequent withdrawal as a COVID treatment. Regulations exist for a reason; it should be recalled that but for the alertness of Dr Frances O. Kelsey enforcing regulation, there would be a generation of limbless Americans due to thalidomide.

To conclude, the rapid production of clinical guidance when facing a new, rapidly spreading and potentially life-threatening disease represents a huge challenge. While awaiting the production of strong evidence by appropriate clinical studies, guidance can be obtained by consensus among relevant stakeholders. However, it must be kept in mind that the lack of evidence can make it difficult to reach a consensus. Indeed, the CORE process was developed initially to identify areas where strong agreement suggested that available evidence was sufficiently clear to alleviate the need for formal evidence assessment. In addition, a perfectly reasonable consensus can turn out to be wrong. When consensus-based guidance is developed, transparency of all steps and procedures as well as detailed narrative explanations of the resulting propositions are crucial to allow readers to understand how to interpret the output. Finally, consensus-based guidance developed before evidence generation always needs to be complemented as soon as possible (*i.e.* when reliable data become available) with evidence-based recommendations, since even an extraordinarily strong consensus can go in the wrong direction. In the interval, their results need to be considered with appropriate caution. Importantly, GRADE-based recommendations on COVID-19 pharmacological treatment are currently being developed by the ERS following the release of several trials, a credit to the high-quality research in this area. Regarding the specific issues of post-hospital follow-up

and rehabilitation, the formulation of (lack of) propositions should not obscure that panels seem to agree that, ideally, patients discharged from the hospital should be systematically followed to identify those with long-term impairments requiring rehabilitation and maybe other therapeutic interventions that remain to be defined. Similarly, they seem to agree that all patients with such impairments should ideally be referred to comprehensive rehabilitation programmes. The best modalities of follow-up (questionnaires +/- lung function and CT-scan +/- exercise testing and echocardiography…) remain to be more precisely defined, maybe using decision trees based on the findings at each step. Then policy makers need to optimise resource allocation to fill the gap between the ideal post-COVID-19 management and resource availability, without impairing access to care for the "usual" (non-COVID) patients with chronic respiratory diseases.

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