EDITORIAL

Precision medicine for corticotherapy in COVID-19

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Of the many lessons to draw from the coronavirus disease 2019 (COVID-19) pandemic is the need to implement precision medicine for critical illnesses without delay. COVID-19 was caused by a single pathogen (SARS-CoV-2) and seemed to follow a homogenous 3-phases time course corresponding to viral replication followed by hyperinflammation and then recovery with or without sequels or death. However, clinical observations highlighted substantial heterogeneity in individual host responses to the virus. Analyses of the dynamic courses in critical COVID-19 discovered that temperature [1] or ventilatory ratio and mechanical ventilation power [2] trajectories enable prognostic enrichment for mortality, excessive inflammatory response, or persistent ventilatory-dependency. While several interventions have favorably impacted the prognosis of COVID-19 patients, there is still substantial heterogeneity in individual responses to these treatments. As an illustration, treatment with corticosteroids variably increased the chance of survival or harmed hospitalized COVID-19 patients during the first wave in 2020 [3]. During the subsequent pandemic waves, the use of corticosteroids was informed by evidence-based guidelines [4], with high compliance of physicians to these guidelines [5]. In this issue of the journal, Torres et al. highlighted the substantial heterogeneity in response to corticosteroids in a large cohort of critical CO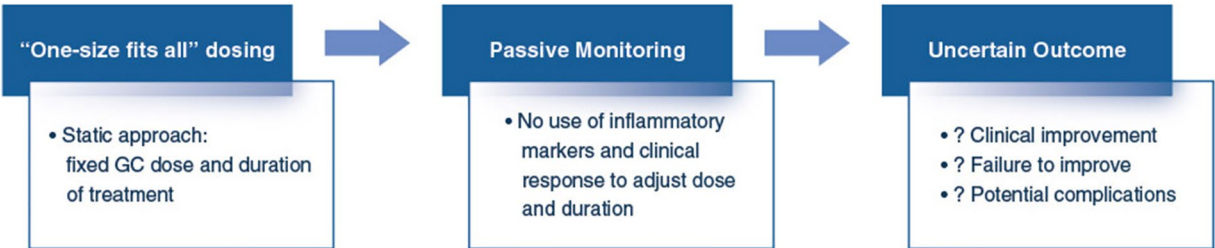VID-19 patients [6]. On the whole population, corticotherapy led to a significant increase in 90-day survival. Patients older than 60 years and the sickest ones based on illness severity scores or the need for invasive mechanical ventilation were the more likely to get survival benefits from corticosteroids. The authors also found that early initiation of corticosteroids was associated with an increased risk of dying and a longer duration of treatment (10 days or more) with increased chance of survival. Taking together information from a systematic review of randomized trials [4] and large and low risk of bias observational cohorts [5, 6], the need for mechanical ventilation is a strong predictor of survival benefits from corticotherapy, and too early (<7 days from infection) treatment initiation is a strong predictor of harm. Based on RECOVERY data [7], one additional life was saved for every 36 patients treated with corticosteroids. In patients with respiratory support, one additional life was saved every 17 patients treated, but in those who did not require oxygen support, one additional death was observed every 27 patients treated. Therefore, there is an urgent need to increase interventions efficiency by rigorous selection of eligible patients in a precision medicine approach. In sepsis, applying various artificial intelligence methods enabled the selection of subgroups of patients drawing optimal survival benefits from corticosteroids [8]. In COVID-19 related acute respiratory distress syndrome (ARDS), using latent class analyses, a 2-class model provided the best fitting population [9]. Patients in the class 2 subset were characterized by a hyperinflammatory profile and a higher risk of death. This study showed a significant interaction between ARDS class and response to corticosteroids with a lower risk of death in the hyperinflammatory phenotype and a higher risk of death in the hypoinflammatory phenotype. There are three prerequisites for corticosteroids to save patients' lives (Fig. 1). First, the main action of glucocorticoids is to counteract proinflammatory signaling in

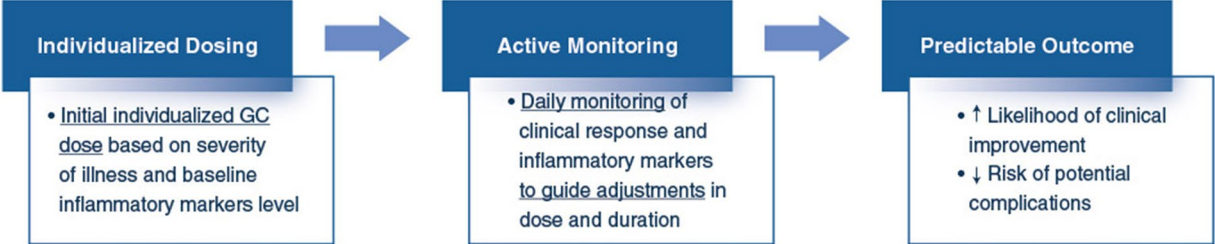*Correspondence: djillali.annane@aphp.fr
[1] Service de Médecine Intensive-Réanimation, General Intensive Care Unit, Raymond Poincaré Hospital (APHP), FHU SEPSIS, U1173, School of Medicine Simone Veil, Université Versailles Saint Quentin, University Paris Saclay-Campus UVSQ, INSERM, 92380 Garches, France

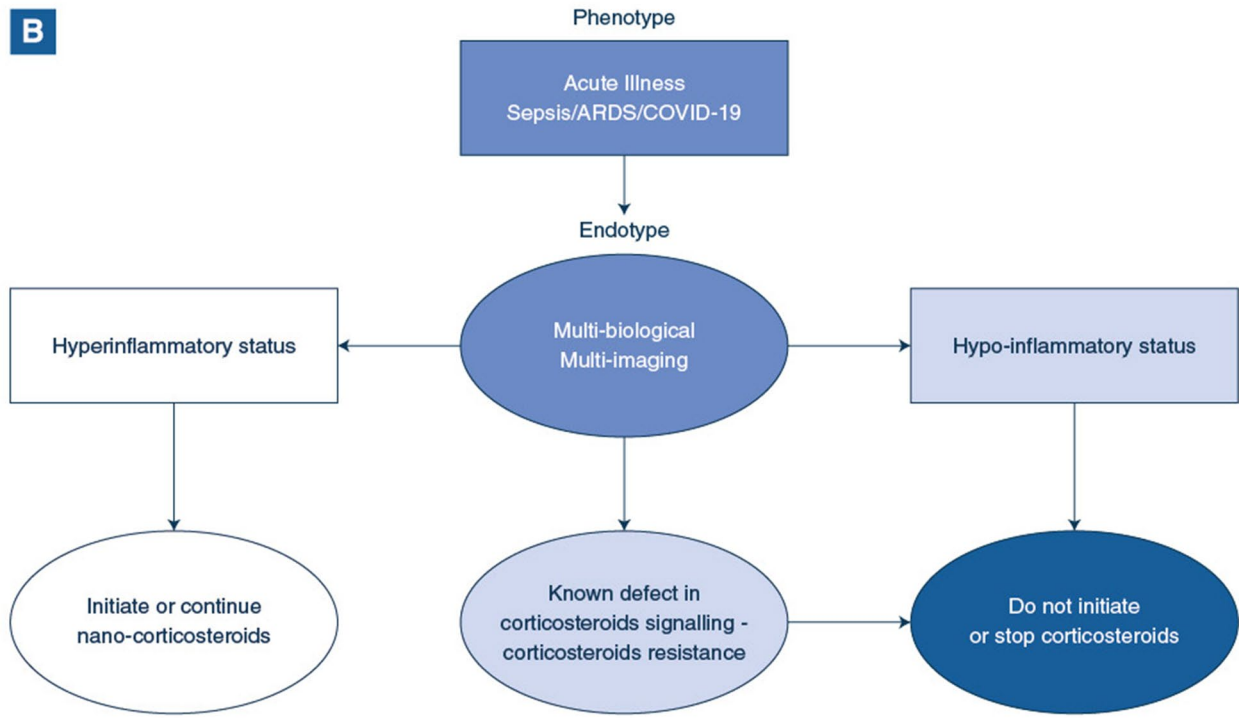Full author information is available at the end of the article

A

"One-size fits all" dosing	Passive Monitoring	Uncertain Outcome
• Static approach: fixed GC dose and duration of treatment	• No use of inflammatory markers and clinical response to adjust dose and duration	• ? Clinical improvement • ? Failure to improve • ? Potential complications

--- PROPOSED NEW APPROACH ---

Individualized Dosing	Active Monitoring	Predictable Outcome
• Initial individualized GC dose based on severity of illness and baseline inflammatory markers level	• Daily monitoring of clinical response and inflammatory markers to guide adjustments in dose and duration	• ↑ Likelihood of clinical improvement • ↓ Risk of potential complications

B

Phenotype

Acute Illness
Sepsis/ARDS/COVID-19

Endotype

Multi-biological
Multi-imaging

Hyperinflammatory status

Hypo-inflammatory status

Initiate or continue
nano-corticosteroids

Known defect in
corticosteroids signalling -
corticosteroids resistance

Do not initiate
or stop corticosteroids

Fig. 1 (See legend on next page.)

response to stress. Then, the patient's response to SARS-CoV-2 has to be characterized by excessive systemic inflammation. Second, all the steps from corticosteroids delivery to inflamed tissues to end-products of intracellular glucocorticoids signaling pathways remain intact [10]. A precision medicine approach to corticotherapy for COVID-19, sepsis, or ARDS requires developing reliable signatures integrating information of the individual patient's immune response and molecular integrity of corticosteroid signaling. It also requires accurate tools to monitor these signatures in real-time and at the bedside. The most important gap to fill is the development of companion tests for corticotherapy in acute inflammatory diseases. Third, as shown by Torres et al. [6], the dosage, the timing of initiation, and the duration of treatment are all essential elements to achieving an optimal response to therapy. Great interindividual variability in both (i) intracellular glucocorticoid receptor sensitivity during corticotherapy [11, 12], and (ii) achieved blood drug levels [13] is an important determinant of response to treatment. We do not have a readily available test to identify corticosteroid resistance; however, a higher corticosteroid dose may overcome decreased corticosteroid sensitivity [11]. Even if we improve our ability to identify responders, interindividual variability remains. In response to corticosteroid treatment, rapid vs. slow inflammatory cytokine reduction results in rapid vs. slow physiological improvement [14]. For these reason,s dose adjustments may have an important role in overcoming interindividual variability. Possibly, a better approach is personalized treatment directed by combined clinical and laboratory variables, not different from what we do with mechanical ventilation and vasopressor support. Close monitoring of clinical response and markers of systemic inflammation should guide the adjustment of dose and duration of treatment [15]. Precision medicine relies not only on enriched endotypes but also on tailoring treatment delivery to target cells or tissues. To this end, nanoparticles may be of potential interest. In a preclinical model of sepsis, leukosomes, leukocytes-derived nanovesicles, were used to encapsulate dexamethasone and deliver the drug precisely at the level of the inflamed vasculature [16]. This approach enabled enhanced dexamethasone therapeutic activity with faster resolution of inflammation and higher survival rates. The future of corticotherapy in acute inflammatory diseases is likely to be characterized by combined enriched endotyping for patient selection and nanomaterials encapsulating corticosteroids to better select target cells/tissues.

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Declarations

Conflicts of interest
Da and GUM have no financial conflict of interest in relation to this topic.

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