In summary, we report the maternal and fetal outcomes of 32 pregnant women in a multicenter cohort study of geographically diverse critically ill patients with COVID-19. In contrast to nonpregnant women of childbearing age, all pregnant women survived, and there were no fetal deaths. Treatments and outcomes, including receipt of invasive mechanical ventilation, the incidence of acute organ injury, and ICU and hospital length of stay, were generally similar between pregnant and nonpregnant women. Pregnant women had high rates of preterm delivery and cesarean section—primarily for the indication of critical illness. Our finding that 13 pregnant women survived to hospital discharge without delivery raises an interesting question of whether or not delivery is required for nonobstetric indications among critically ill pregnant women (10). Additional data are needed in critically ill pregnant women with COVID-19 to help inform clinical practice. ■

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What Sepsis Researchers Can Learn from COVID-19 ⭐

To the Editor:

Despite intensive research efforts, the search for new therapeutic options for sepsis has yielded no result (1). However, the ongoing coronavirus disease (COVID-19) pandemic shows that effective therapeutic options for the distinct subgroup of viral sepsis due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can be found within months (2). What can sepsis researchers learn from the way COVID-19 is studied?

Heterogeneity

In clinical practice, recognition of the wider sepsis syndrome can improve awareness and timely initiation of treatment. However, when looking for new therapeutic options in a research setting, this broad approach may be less desirable. One of the questionable tenets of sepsis research has been whether the host response in sepsis represents a "final common pathway" irrespective of the source of infection or causative pathogens (1). This would justify looking at the broader sepsis population in research, with the added benefit of having larger study cohorts. However, most believe that the host response is just too complex and that a "final common pathway" may simply not exist (1). The resultant heterogeneity within the sepsis population is therefore considered to be a major limiting factor in finding specific sepsis therapies (1, 3). Extensive efforts have thus been made to reveal homogeneous sepsis subgroups (1, 3, 4).

Shared and distinct gene expression profiles are found when pulmonary and abdominal sepsis are compared (3), suggesting that part of the heterogeneity in the sepsis population could be explained by the infection site or invading pathogen. Several other studies that aim to find homogeneous sepsis subgroups through

various methods show different distributions of infectious etiology across the newly formed subgroups, again implying that infecting organisms are associated with differences in the host response (3). One study even states, "we examined only datasets of patients with bacterial sepsis at admission, because the clustering algorithms may otherwise have been overwhelmed by the differing host responses to different types of infections" (4).

In contrast to the many different causative microorganisms and arguably differing host responses in sepsis, early COVID-19 studies show comparable gene expression profiles in their populations, such as the upregulation of chemokines and neutrophils (2, 5). This is possibly one of the key reasons why there have already been positive randomized trials with therapeutic options for COVID-19 (2). Despite mixed results in sepsis trials, dexamethasone treatment resulted in lowering of 28-day mortality in COVID-19, particularly in patients who received respiratory support (2). Perhaps focusing on a single site of infection or infective agent took away much of the heterogeneity. Researchers in the field of sepsis may learn from this and adapt current research paradigms and trial designs in such a way that stratification per infection type is possible and statistically meaningful.

Outcome Measures

Outcome measures for sepsis clinical trials have been frequently discussed. Trials using novel therapeutic options have failed to demonstrate a benefit in general outcomes such as rates of ICU admission or mortality (1). In 2005, the International Sepsis Forum proposed that sepsis researchers should widen the breadth of outcome measures that are used in clinical trials (6). Mortality is an attractive outcome measure, but other patient-centered benefits such as quality of life and long-term morbidity should not be overlooked. The International Sepsis Forum colloquium provided additional clinically relevant possibilities to show the benefits of a treatment (6). Nevertheless, the literature on new therapeutics for sepsis continues to be dominated by the search for short-term mortality benefits.

For COVID-19, the World Health Organization (WHO) recognized that a core set of outcome measures was needed to investigate this new disease and compare outcomes globally. Experts who proposed the outcome measures for sepsis in 2005 also did so for COVID-19 in 2020 (7). This time, a minimal common outcome measures set was used globally.

Another advantage of focusing on a more defined disease state, such as SARS-CoV-2 infection, in contrast to all-cause sepsis, is that site-specific outcome measures can be used. For instance, the Murray score to assess lung injury (7) or diffusion capacity to assess pulmonary function (8) are valuable outcomes that could potentially be improved by certain treatments. Obviously, it does not make sense to assess pulmonary function as an outcome in all sepsis patients.

Global Collaboration

Just weeks after the COVID-19 outbreak in Wuhan, China, the WHO coordinated a global research roadmap (9). Experts from various fields agreed on key questions and strategies to accelerate research. The WHO launched a COVID-19 Data Platform to collect global data through a predefined case report form (CRF) (9). When patient data was collected with this CRF anywhere around the world, the same variables were documented, and the criteria for COVID-19 diagnosis (e.g., PCR or computed tomography scan) were available. The CRF was widely adopted and created a unique opportunity for global collaborative efforts, with minimal missing data or different inclusion criteria.

Furthermore, global genomic alliances are providing insights into how clinical and immunological manifestations of infection, and its natural variability, are governed by human genetics. In this case, global collaborations help find specific individuals prone or resistant to disease, who are especially interesting when trying to elucidate pathophysiological mechanisms.

Besides the use of a standardized data collection, COVID-19 research further profiled itself through the use of popular messaging platforms such as Slack (10). In the United States, a group of researchers created a Slack forum to coordinate research projects across the country, providing yet another opportunity to have comparable study results.

Pitfalls

The COVID-19 pandemic created much urgency with researchers worldwide. So far, we have outlined positive aspects of the COVID-19 research field from which sepsis researchers can learn (Table 1). Inevitably, this urgency also created pitfalls. The pressure to quickly perform and publish new studies led to acceptance of flexibility in protocols and trial design, shorter turnaround times for peer review at medical journals, and omission of extensive

Table 1. Key Aspects of COVID-19 Research from Which Sepsis Researchers Can Learn

Aspect	Message
Heterogeneity	COVID-19 is more homogenous than sepsis, and that has probably been helpful with identifying effective treatments. Sepsis researchers should therefore consider smaller/more homogenous subgroups for study.
Outcome measures	Widespread use of core outcome sets facilitates comparison and pooling across studies. Examples of core outcomes are as follows (7): • Organ dysfunction • Biochemical parameters • Radiological findings • Duration of intervention • Quality of life • Resource use Examining homogenous subgroups facilitates additional outcome measures (e.g., severity of lung injury) that would not be relevant to an all-cause sepsis population.
Global collaboration	Global data platforms with a standardized case report form can facilitate pooling of sepsis research. National or global coordination of large research projects can streamline sepsis research. Popular messaging platforms can be excellent tools to aid trial coordination.

Definition of abbreviation: COVID-19 = coronavirus disease.

testing in preclinical animal models. Although these practices speed up the research process, one should be aware that they can also lower the standard of medical research, as is evident by the retraction of several papers in prominent medical journals over the past months. ∎

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Comparing Nasopharyngeal and BAL SARS-CoV-2 Assays in Respiratory Failure

To the Editor:

Patients with acute respiratory failure concerning coronavirus disease (COVID-19) require a prompt, accurate diagnosis for appropriate triage and management. PCR assays for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA can be performed on upper or lower respiratory samples. Nasopharyngeal (NP) and BAL have generally good concordance for viral respiratory infections (1). However, reports have described patients diagnosed with SARS-CoV-2 by BAL after initial negative NP testing (2). We studied a series of patients who were critically ill with a clinical concern for COVID-19, who had NP and BAL PCR testing to determine NP and BAL test characteristics and accuracy.

Methods

We retrospectively reviewed adult patients intubated for acute hypoxic respiratory failure with a clinical concern for COVID-19 who were tested with both NP and BAL PCR assays for SARS-CoV-2 RNA. We included patients who had BAL assays performed within 5 days after an NP assay, and BAL was considered the definitive diagnostic assay. Statistical analyses were performed with Microsoft Excel version 15.39 for macOS (Microsoft) and in GraphPad PRISM 8 (version 8.4.3 for macOS). Mann-Whitney tests were used to compare nonparametric groups. The study was approved by our institutional review board (STU00212283).

Results

We reviewed 123 patients intubated for acute hypoxemic respiratory failure and tested for SARS-CoV-2 with a BAL test within 5 days after an NP test. The median duration between an NP and a BAL swab was 1 day (interquartile range, 1–2.75 d). The NP tests were run on the following platforms: 52 Abbott ID NOW, 5 Becton-Dickinson, 28 Cepheid, 33 in-house, and 5 not listed. The BAL tests were run on the following platforms: 0 Abbott ID NOW, 10 Becton-Dickinson, 84 Cepheid, and 29 in-house. The median age was 63 (interquartile range, 46–70) years, and 39 (31.7%) were female. Overall, 79/123 (64.2%) patients ended up having COVID-19.

Seventy cases had both NP and BAL tests positive; 39 cases had both NP and BAL tests negative; 5 cases had positive NP and negative BAL; and 9 cases had negative NP and positive BAL (Table 1). In comparison with BAL, sensitivity of an NP assay was 88.6%, specificity was 88.6%, positive predictive value was 93.3%, negative predictive value was 81.3%, and accuracy was 88.6%. Of the 14 discordant NP and BAL cases, the NP tests were performed on 6 Abbott ID NOW, 2 Becton-Dickinson, 4 Cepheid, and 2 in-house–developed PCR platforms, whereas the BAL tests were performed on 2 Becton-Dickinson, 11 Cepheid, and 2 in-house