How a trial that mirrors intensive care practices is pinpointing life-saving coronavirus treatments

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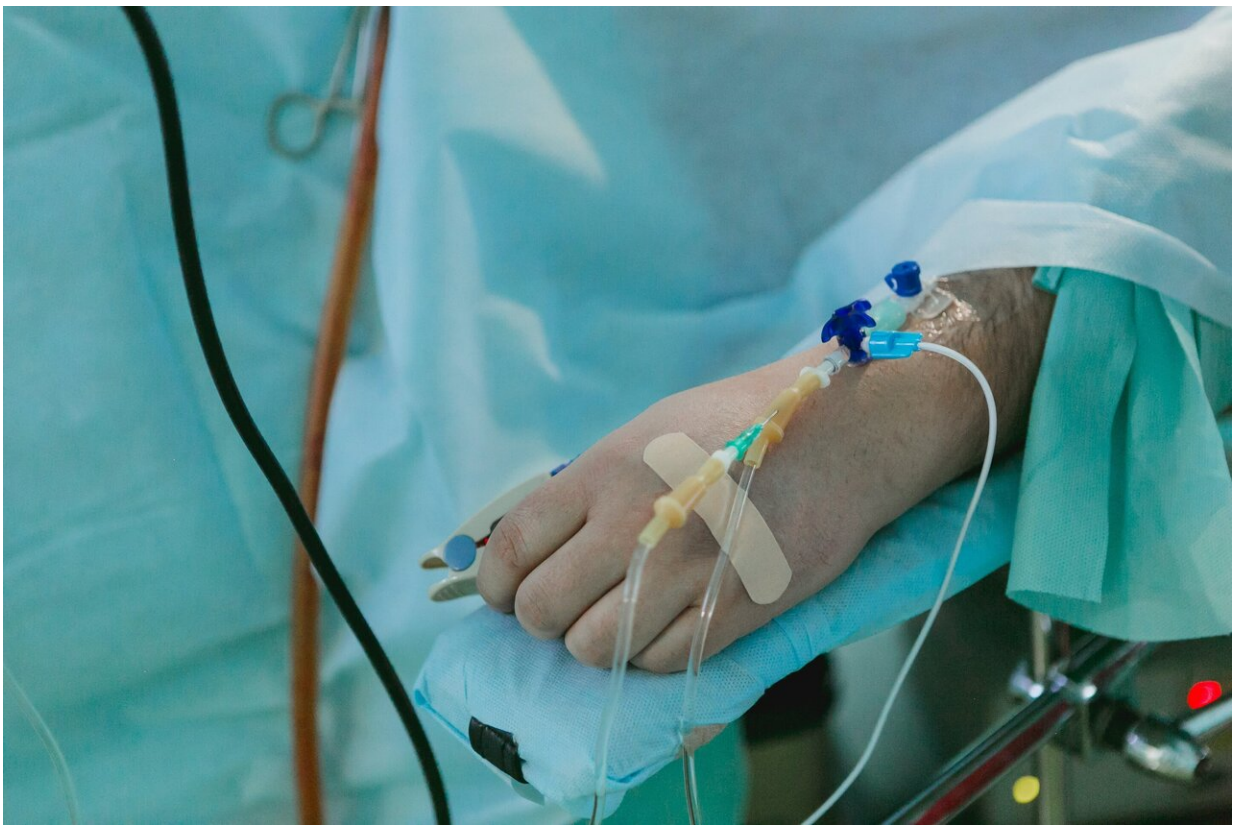

Identifying which treatment is effective in severely ill patients can be difficult as they undergo multiple interventions. Credit: Olga Kononenko/Unsplash

Two anti-inflammatory drugs—tocilizumab and sarilumab—as well as

steroids, have been identified as potential life-saving coronavirus treatments thanks to a trial set up in the wake of the 2009 swine flu pandemic that mirrors the way that people receive multiple treatments while in intensive care.

When the H1N1 swine flu outbreak hit in 2009 it caused typical flu symptoms, but severe cases led to pneumonia and lung failure.

Doctors were unsure which treatments would work, but steroids, which dampen down inflammation, seemed like a good bet. Clinicians in intensive care units decided to set up a trial to see if steroids helped patients severely ill with swine flu.

But this proved impossible. "The pandemic came and went and we missed an opportunity to test whether even a simple intervention like steroids worked or not," said Professor Alistair Nichol, ICU doctor in St Vincent's University Hospital in Dublin, Ireland, who worked in an Australian hospital during the 2009 pandemic.

"There was a peak in intensive care unit (ICU) transmissions and some clinicians got frustrated in trying to set up a drug trial (that never happened)," recalled Dr. Lennie Derde, an intensive care doctor at UMC Utrecht in the Netherlands.

That pandemic killed tens of thousands of people, but ICU clinicians expected worse in the future. "This one was moderately bad," recalled ICU physician Professor Steve Webb at the Royal Perth Hospital in Australia, 'but if we had a really bad one, we were just woefully unfit to be able to do drug trials." So ICU clinicians came together to be better prepared. "Nobody doubted there would be a next time," said Prof. Nichol.

Community-acquired pneumonia

Typically, a viral pandemic begins with a spike in unusual pneumonia cases in ICUs.

In March 2020, patients flooded ICUs with SARS-CoV-2 infections. This time, some ICU clinicians were ready from the get-go. A number of coronavirus patients were quickly recruited into an existing clinical trial calledREMAP-CAP, set up in the wake of the 2009 swine flu outbreak, to test which drugs worked on their pneumonia.

It was 'set up in peacetime," explained Prof. Nichol, 'so as to be ready for wartime if a pandemic was to arrive."

"We were able to flick the switch to include pandemic patients," said Dr. Derde. "That is why we were able to include our first patient on the 9th of March."

The trial tests various drugs—rather than the usual one or two—for community-acquired pneumonia, with all the regulatory and ethical approvals in place. Itwas set up by a project called PREPARE for patients suffering from severe community-acquired pneumonia caused by bacteria or viruses, which kills about one in five people with it in ICU, although the figures can be much higher.

Results on steroids from the trial contributed to the World Health Organisation recommending them for COVID-19 patients in September 2020. By then, REMAP-CAP, which now involves about 300 hospitals, was testing lots of interventions (it currently has 31).

Doing this sets it apart from a traditional randomised controlled trial, which is the gold standard to prove whether a drug is effective or not. Patients are usually given either one or two drugs or a placebo, and then outcomes are compared. REMAP-CAP is different—and more flexible—in that it tests many types of treatments at the same time. One

patient can receive multiple interventions, which is not unusual for someone severely ill. A regimen of treatments is 'much more in line with your typical clinical treatment," said Dr. Derde, who is the European coordinator of the trial.

The clinical trial design means that 'we can analyse the interactions between drugs, which is a huge advantage in a pandemic," she said.

"A single COVID patient can be randomised for up to eight separate aspects of their treatment," said Prof. Webb. "We're obviously learning much more quickly, because we're testing so many different things simultaneously." A patient is enrolled in one treatment 'domain," and then is randomly assigned to one of a handful of interventions in that domain.

The 12 different 'domains' of treatment include anti-coagulation treatments, anti-inflammatory drugs, and immune modulating drugs. "One patient might be involved in six or seven different domains of the trial," said Prof. Nichol. In fact, this better reflects how a patient with COVID-19 is treated in hospital, according to the doctors.

Monoclonal

A big result—presented in a pre-print study, so not yet peer reviewed—is that two monoclonal antibodies (tocilizumab and sarilumab) reduced death from COVID-19 in severely ill patients, and time spent in ICU. Those benefits seem to be on top of those from steroids, says Prof. Webb.

Tocilizumab and sarilumab block a chemical signal called interleukin-6 (IL-6), which stokes inflammation. In severe COVID-19, the inflammatory response of a patient's immune system begins to damage body tissue, in friendly fire, while attacking the virus. There was

therefore good reason to think the drugs might be effective.

Indeed, once a new disease turns up, and its mechanisms are reported, an array of medications will be considered by physicians. But they do not know which ones work. The results for COVID-19, explains Prof. Webb, 'was quite a scattergun approach of clinicians using repurposed medicines."

Sometimes, as in the case of the malaria drug hydroxychloroquine, a small study and lots of hype persuades some that an old drug is worth a try. But it requires a large clinical trial, such as REMAP-CAP, which involves 6,000 patients, to show whether that drug is safe and effective. Physicians can now prescribe the IL-6 blockers and steroids with greater confidence, while hydroxychloroquine is left on the shelf.

Indeed, finding that a drug does not work, or causes a negative effect, can be equally beneficial. "The anti-virals and the anti-coagulants have not just been ineffective, but may result in worse outcomes for patients," said Prof. Webb, about recent preliminary findings. "It is just as important to identify treatments that are harmful."

It is difficult for a physician to know whether a drug is helping or hindering their patients. "For an individual doctor at a patient's bedside, it can be hard to tease out if giving someone something helped or if they would have gotten better anyway," explained Prof. Nichol. Severely ill patients usually receive multiple interventions, which makes knowing which treatment was effective tougher.

Combinations

The REMAP-CAP trial was created to be multifactorial, meaning that the effects of many different treatment combinations on patients can show up in the data. Bayesian statistics, which applies probabilities to

statistical problems, makes sense of all the data to answer crucial questions, such as when a treatment reaches a positive result, or if it is shown not to work, or if there are positive interactions between drugs. Such a strategy with multiple treatments had been used for cancer, but never a global ICU study.

At the heart of these trials is a simple fact: it is impossible to guess which treatments will work. Small studies can be biased and inconclusive, which is why large randomised trials are needed.

"Years ago, I used to think that there were things that definitely would work, and then they didn't," said Prof. Webb. "I've been doing clinical trials for so long now that the only thing I am confident of is that, when you do trials, you will get surprises."

Dr. Derde praises the European Union's actions in 2014 'because they funded the European part of what is now REMAP-CAP, with the vision that they needed to set up an infrastructure for pandemic research." Other funders around the world, from Australia to New Zealand to Canada and the US, subsequently joined the effort.

REMAP-CAP is an international effort now, with 300 hospitals taking part in about 20 countries, testing out 31 different interventions. The trial will continue to prove which treatments work in severely ill COVID-19 patients. As the virus surges in many countries and until the vaccine rollout can control the pandemic, proven drugs are needed to save lives.

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