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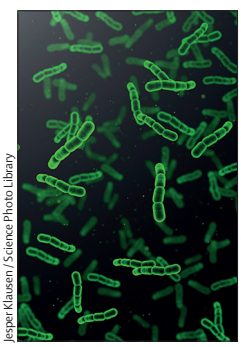
One step closer to precision medicine for infectious diseases



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In *The Lancet Infectious Diseases*, Pierre-François Laterre and colleagues[1] present the promising results of a first-in-human study of CAL02, a novel antitoxin liposomal agent administered as an adjunct to antibiotic therapy in severe community-acquired pneumococcal pneumonia. Two doses of CAL02 were administered, with a 24 h interval. CAL02 consists of a mixture of small, empty, uncoated unilamellar liposomes that act as traps for a broad panel of bacterial toxins known to be inserted in cellular membranes.[2] Despite this study[1] only enrolling 19 patients into three groups (placebo, low-dose CAL02, and high-dose CAl02), more positive patient outcomes were observed in the high-dose CAL02 group compared with placebo. The advantages of CAL02 treatment were particularly obvious during the early course of the infection, when the bacterial load is high. We consider this study a medical breakthrough for two reasons.

First, animal and clinical studies have suggested that early sepsis mortality is caused by inflammation and infection-associated organ failure, whereas late mortality is due to immunosuppression, intensive care unit-acquired complications, and end-of-life decisions.[3,4] One possible reason for the low effectiveness of antibiotics on early mortality is that such drugs can kill toxin-producing bacteria but are unable to inactivate already-secreted toxins. Therefore, inhibition of toxin action might help to decrease early patient deterioration. Notably, there are several examples of toxin-targeted adjunctive treatments in patients with sepsis currently under development, such as extracorporal toxin adsorption and IgM-enriched immunoglobulins.[5-7] However, these treatments do not specifically eliminate bacterial toxins. They also inactivate damage-associated molecular patterns and pathogen-associated molecular patterns. Furthermore, extracorporal absorption removes pro-inflammatory cytokines.

Second, the global emergence of antibiotic resistance and the insufficient number of novel antibiotics are a major public health concern.[8] Accelerated development of novel antibiotics and antibiotic stewardship will certainly be of value in this crisis, but will not resolve it once and for all. Antibiotics kill bacteria and therefore impose selective pressure on the evolution of antibiotic resistance genes, not only in pathogens but also in the microorganisms that constitute a patient's microbiome. Microbiomes have been identified as a major reservoir of resistance genes that can be acquired by pathogens via horizontal gene transfer.[9] Consequently, many antibiotics can only be safely used for 15–20 years before resistance emerges.[10] Thus, we are trapped in a biological arms race between novel antibiotics and emerging resistance. A possible disruption of this vicious cycle could be achieved by non-lethal precision drugs that avoid collateral damage and inactivate or disarm the pathogen without killing. These requirements are fulfilled by virulence blockers, which target bacterial adhesion, bacterial toxins, or the quorum sensing system, resulting in decreased virulence without killing the pathogen or causing damage to the microbiome.

Although virulence blockers are a current focus of research into anti-infectives, the principle underlying them was originally discovered more than 120 years ago by von Behring and Kitasato, who observed that serum from vaccinated animals could inactivate those toxic compounds produced by tetanus bacilli.[11] In those days, clinical development moved more quickly than today. von Behring and Kitasato's research was published 11 days after their decisive experiment was completed; their first-in-human study was done 1 year later and, despite some drawbacks due to dosing issues, Hoechst started to produce and distribute the serum in 1892.[11] These results paved the way to tetanus and diphtheria toxoid vaccines that are still in use today.[11] Over time, the clinical use of CAL02 might also help to identify certain toxins with major contributions to the severity of infection, which can be further evaluated as vaccine targets.

There are dozens of virulence blockers in the early stages of clinical development and some have already received US Food and Drug Administration approval;[12]

however, questions remain unanswered. If virulence blockers are used only in combination with antibiotics, as in the current study,[1] the theoretical advantage of avoiding selection of antibiotic resistance genes cannot be harnessed. Furthermore, the species-dependent or even strain-dependent activity of antibody-derived toxin inhibitors is a large obstacle to overcome when it comes to empirical treatment, and therefore requires rapid in-depth pathogen diagnostics. However, pathogen diagnostics is also evolving, as the first studies using next-generation sequencing to detect pathogens directly in clinical samples are underway.[13]

Most of the virulence blockers under development are antibodies or antigen-binding fragments, reflecting von Behring and Kitasato's approach. Very few virulence blockers have been described to date that do not resemble this principle, and, to our knowledge, the present study is the first completed clinical trial. Therefore, CAL02 represents a milestone, since it is the first non-antibody-based virulence blocker that has successfully overcome this hurdle of a clinical study and it appears to inactivate a broad range of secreted toxins, making it potentially suitable for adjunctive empirical treatment.

At last, we might be one step closer to precisely targeting pathogens without inflicting selective pressure and damaging the microbiome. Nevertheless, compared with the rapid translation of novel principles into clinical practice 120 years ago, clinical development processes in the present day are highly regulated and have many pitfalls. We keep our fingers crossed that CAL02 will not get lost on its way to the patients who need it.

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We declare no competing interests

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A step further in a vaccine for *Escherichia coli*

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Extra-intestinal pathogenic *Escherichia coli* (ExPEC) are responsible for almost as many severe infections as pneumococci or meningococci. Estimates of *E coli* bacteraemia and sepsis in the health-care system in the USA suggest that more than 85 000 deaths are due to *E coli* sepsis.[1] Additionally, multidrug resistance is an increasing problem, especially in *E coli*, and even more pronounced in severe infections, such as urosepsis.[2] Alternative anti-infective strategies, such as a specific vaccine against ExPEC, would definitively increase the options for the treatment of invasive *E coli* disease and could be considered a great clinical advantage and contribute to decreasing antibiotic selection pressure.

Serum resistance is an important virulence property of bacteria in invasive infections, because blood serum is otherwise highly toxic to most bacteria. ExPEC strains are characterised by a high resistance to serum.[3] Serum resistance is due to resistance to the complement system and is affected by the length of the O-antigen and its type.[4] Although the O-antigen represents a