

Improving the fate of severely infected patients: the promise of anti-toxin treatments and superiority trials

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1. Introduction

Severe infections requiring immediate admission to special units in hospital, and involving intravenous antibiotics and supportive therapy such as fluids or vasopressors, are still associated with unacceptably high mortality rates. A retrospective overview, spanning the past decade, of the performance of new antibiotics is dismaying indeed. Novel approaches and new regulatory paths to develop treatments that will significantly improve the fate of severely infected patients are urgently needed.

2. Anti-toxin agents defy the most alarming infections

Novel treatments targeting bacterial components responsible for complications and death, such as bacterial toxins, may be game-changers in the field of antibacterial medicines. The first anti-toxin drug, bezlotoxumab (Zinplava™ from Merck & Co., Inc.), a human monoclonal antibody targeting *Clostridium difficile's* toxin B, was approved in 2016 [1]. Several anti-toxin agents are in clinical development, including monoclonal antibodies targeting *Staphylococcus aureus'* α -toxin (MEDI4893 from MedImmune LLC, AR-301 (Salvecin™) from Aridis Pharmaceuticals, Inc. and ASN100, which also targets leukocidins, from Arsanis, Inc.). Other monoclonal antibodies target *Pseudomonas aeruginosa's* type III toxins secretion system (MEDI3902 from MedImmune LLC). A broad-spectrum anti-toxin liposomal agent (CAL02 from Combioxin SA) is also in clinical development.

Bacterial toxins play a critical role in bacterial growth and are directly responsible for serious infection-related complications [2]. For example, *S. aureus'* α -toxin directly disrupts the epithelial barrier function, promotes invasiveness, and harms immune cells [3]. In similar mechanistic ways, the toxin effectors of *P. aeruginosa's* type III secretion system intoxicate pulmonary epithelial cells, impair innate immune responses, and compromise tissue barriers, thus promoting bacterial dissemination to the bloodstream and sepsis [4]. *Streptococcus pneumoniae's* pneumolysin also plays an integral role in the disease and in the development of severe and fatal complications by affecting tissues' integrity, by contributing to edema

and hemorrhage, and by altering the balance of local and systemic immune responses [5,6]. Bacterial toxins may therefore cause pathophysiological reactions leading to septic shock, they are the cause of extended hospitalization and tremendous increases in costs of care, and they are linked to the worst outcomes in human infections.

Antibiotics effectively kill the pathogen but fail to neutralize toxic components produced. As an example, in fighting severe community-acquired pneumonia as stand-alone treatments, antibiotics prove to have limits. Indeed, mortality rates in adult patients admitted to the ICU may still reach 40% regardless of antibiotic resistance, and lethal complications, such as organ failure and septic shock, occur when tissues are already pathogen-free and the pulmonary process is clearing [7]. Anti-toxin agents, as an adjunctive therapy, may complement the action of antibiotics to defy the most alarming infections. Moreover, while anti-toxins have no direct bactericidal activity, they have been shown to lead to a significant reduction of bacterial load, probably by depriving bacteria of the mechanisms they use to feed and multiply and by acting as a shield for the immune system, which can then clear the infection more appropriately [8,9]. By disarming the pathogen rather than killing it, non-antibiotic approaches do not impose selective pressure on bacterial growth and may therefore offer a long-term solution to the problem of resistance and a chance for a wiser use of antibiotics.

3. Improvement in outcome relies on superiority

The regulatory guidance for the clinical development of anti-toxin drugs for the treatment of severe infections still needs to mature. For antibiotics, regulatory agencies have favored the use of active-control non-inferiority trials, that is, clinical studies demonstrating that the new drug or regimen has approximately the same efficacy as the active comparator within a predefined non-inferiority margin. The new drug may offer other benefits such as a better safety profile, fewer administrations, or a lower price. However, a retrospective overview of the past decade draws attention to the inability of new antibiotics to significantly decrease mortality rates, as mentioned above, or to demonstrate superiority in clinical cure. For instance, results obtained in numerous pivotal phase-3 clinical trials carried out in the last 13 years, with new antibiotics

against skin and soft tissues infections, reveal that efficacy in the intent-to-treat population remains unchanged at 80–85% in the assessments of the Early Clinical Evaluation (ECE, as per US FDA requirements) or of the Test of Cure (TOC, as per European Medicines Agency (EMA) requirements) [10–14].

The lack of any significant improvement in efficacy and the steady use of non-inferiority designs for new antibiotics contrast with the situation in other medical areas, such as oncology, for which the most recent approvals (e.g. pembrolizumab or ipilimumab) have been based on the statistically significant superiority of the efficacy of the new agent. In fact, antimicrobial clinical studies constitute the majority of all non-inferiority trials [15].

The context of anti-toxin drugs contrasts with that of antibiotics: anti-toxin agents are used as add-on treatments to antibiotics and standard of care (SOC), they are pharmacologically distinct from the active control, and their clinical evaluation allows patients with a serious or life-threatening bacterial infection to receive any standard active therapy available. Clinical trials need to demonstrate that the new agents add efficacy to existing antibiotic treatments, and these trials need to rule out all cases with inferior efficacy as compared to existing SOC. Clinical trials evaluating a novel anti-toxin agent therefore must aim at evaluating a superiority hypothesis, as opposed to non-inferiority trials, in which a certain inferior efficacy of the new treatment is allowed. In other words, active-controlled superiority studies for novel add-on antimicrobial agents are not only ethically acceptable but are imperative.

While clinical trial designs and the most relevant study endpoints in severe infections have been recently reviewed [16], there is to this day no clear regulatory guidance for combination therapies such as that of anti-toxins in addition to SOC. The recent guideline published, 'Antibacterial therapies for an unmet medical need for the treatment of serious bacterial diseases,' does not include this scenario [17]. Both the FDA and the EMA have nevertheless already stated that for life-threatening diseases or diseases causing irreversible harm, no appropriate non-inferiority margin could be easily justified [18].

Anti-toxin approaches aim directly at patients' greatest interest and hold the potential to provide significant improvement in survival rates in infections that pose the greatest threat, such as hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, sepsis, endocarditis, or osteomyelitis. New regulatory guidelines are therefore eagerly awaited for those novel approaches aiming at a better and not simply non-inferior result.

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Declaration of interest

S Azeredo da Silveira and A Perez work at Combioxin SA Geneva, Switzerland which develops innovative anti-toxin treatments for severe infections. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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