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WHAT'S NEW IN INTENSIVE CARE

Alternatives to antibiotics

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Infection remains one of the main reasons for admission to intensive care units (ICU). As a consequence, more than 60 % of ICU patients receive antibiotics during their stay in the ICU [1], despite implementation of antibiotic stewardship programs to improve the quality of antibiotic use [2, 3]. In most countries antibiotic consumption is mainly driven by pulmonary infections, such as community acquired pneumonia (CAP), healthcare associated pneumonia (HCAP), hospital acquired pneumonia (HAP), and ventilator associated pneumonia (VAP). Bacterial resistance has concurrently increased, especially for Gram negative bacilli, including *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii*, while prevalence of methicillin resistance among *Staphylococcus aureus* has remained stable or declined in most European countries [4]. Yet, very few new antibiotics have been developed over the past decade and only a few novel drugs are in the development pipeline of pharmaceutical companies. To meet the current and emerging unmet medical needs, alternative therapeutic options to antibiotics, including new strategies, have to be considered in the ICU. Among the several non-antibiotic strategies that are currently being investigated in the ICU, we focused on monoclonal antibodies and bacteriophages but some others such as vaccination, immune stimulation, antibacterial peptide, or probiotics could also bring encouraging results in the near future [5].

A promising option is the recent development of monoclonal antibodies (mAbs) that can be used either "prophylactically" through a pre-emptive approach in high-risk (e.g., mechanically ventilated and colonized) patients or used therapeutically when an infection is suspected and a pathogen is known (Fig. 1). Such targeted approaches, which have been hampered in the past by the time required for strain identification using classical culture, are now possible owing to a number of real-time diagnostic platforms, including PCR, that are available or in development [6].

Pseudomonas aeruginosa remains one of the three most frequent Gram negative pathogens causing nosocomial infections in intubated patients and probably the one associated with the highest attributable mortality in nosocomial pneumonia (15 % rising to 35 % in case of multidrug resistance) [7]. Treatment is frequently hampered as a result of its intrinsic resistance to many antibiotic classes and rapid acquisition of new resistance, as well as the presence of virulence factors. Antipseudomonal mAbs may add benefit to conventional antibiotic treatment. In a small-scale trial, repeated doses of a monoclonal antibody targeting *P. aeruginosa* serotype O11 as adjunctive therapy to antibiotics yielded promising efficacy with better clinical improvement in a shorter time in 17 patients with HAP or VAP compared to 14 control patients without observed immunogenicity related to the antibody [8]. More recently, the first trial preemptively using a monoclonal targeting *P. aeruginosa* PcrV revealed encouraging results with a significant decrease of infectious events in mechanically ventilated ICU patients colonized with *P. aeruginosa* [9]. A bispecific mAb targeting both the virulence factors PcrV and Psl of *P. aeruginosa* [10] will be evaluated in a phase II clinical trial in Europe (ClinicalTrials.gov: NCT02696902). In this study the mAb will be used preemptively in ICU patients with documented colonization of the respiratory tract with *P. aeruginosa*. Some other programs evaluating mAbs targeting *P. aeruginosa* antigens are also moving to clinical development.

In the ICU, *S. aureus* is another "bad bug" frequently causing bloodstream, skin, soft tissue, and lower respiratory tract infections, and—as for *P. aeruginosa*—antibiotic treatment can be hampered because of emergence of multidrug-resistant strains. Among the several toxins and virulence factors that *S. aureus* utilizes to induce disease, α-toxin, a pore-forming, cytolytic toxin is

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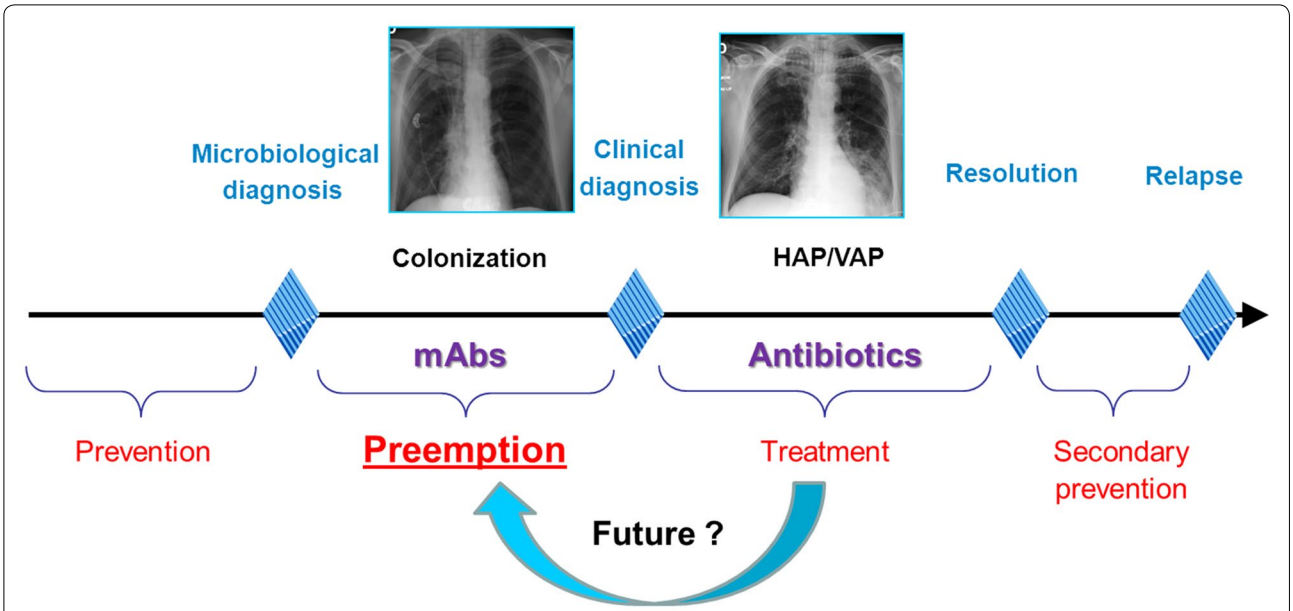

Fig. 1 Different time windows for possible treatment approaches in VAP

considered the key toxin facilitating tissue invasion and necrosis [11]. Human mAbs specifically binding and neutralizing α-toxin of *S. aureus* are currently being evaluated as adjunctive therapy in a phase I "first in human" study in patients with severe VAP (ClinicalTrials.gov: NCT01589185). Furthermore, another mAb targeting α-toxin is currently being evaluated in a phase II trial in mechanically ventilated ICU patients colonized with *S. aureus,* with a targeted population of nearly 500 patients (ClinicalTrials.gov: NCT02296320).

These ongoing studies are focused on *P. aeruginosa* and *S. aureus*, but there is also interest in mAbs targeting other bacteria, such as *A. baumannii* or *K. pneumoniae*, illustrating the interest in such drugs in the ICU, representing not only a true therapeutic revolution but also shifting patient management towards real-time monitoring and pre-emptive immune modulation, rather than antibiotic prophylaxis and treatment.

Bacteriophages have also gained renewed interest as an alternative to antibiotics in the ICU setting. Discovered and used for the first time in the early 1900s, then forgotten through the rise of antibiotics, phage therapy is actually back in clinical development. Phages are natural viruses that kill specific bacteria without action on any other organisms. As compared to antibiotics, their specificity reduces the impact of antibiotic therapy on the natural microbiota. Lytic phages are carefully screened and characterized prior to selection as a drug candidate [12]. Some are currently being evaluated in the treatment of burn wound infections caused by *P. aeruginosa* in a phase I/II clinical study (www.phagoburn.eu; ClinicalTrials.gov: NCT02116010) [13], and case reports claim benefits of combining phages with antibiotics, for instance to fight biofilms [14]. In other studies the safety of an anti-staphylococcal phage cocktail is being evaluated in patients with chronic sinusitis refractory to antibiotics [15] and in patients with staphylococcal wound infections (www.ampliphibio.com). If successful this anti-staphyloccocal treatment could be brought into the ICU setting at least for severe skin infections. The PneumoPhage research project (http://www.pherecydes-pharma.com/pneumophage.html) investigates the action of a phage cocktail against *P. aeruginosa* respiratory tract infection in animal models using a new-generation nebulizer to optimize the administration of the aerosol into the lungs [16]. A similar approach is being developed for cystic fibrosis, and this might represent an adjunctive therapeutic solution in HAP/VAP [17].

The threat of complete absence of effective antibiotics to treat problematic ICU infections is fueling the development of innovative treatment and prophylactic approaches. Within all their potential indications, bacteriophages could in the near future be used in severe pseudomonal VAP through nebulization. Monoclonal antibodies may become alternative treatment options, either as pre-emptive treatment to prevent early staphylococcal VAP mostly in trauma and neurological patients known to be at risk or pseudomonal HAP/VAP, in long-term ICU hospitalized patients, or even as adjunctive treatment in severe ICU infections especially those caused by multiresistant bacteria.

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Compliance with ethical standards

Conflicts of interest
Bruno Francois is the coordinating principal investigator of an ongoing international phase II trial testing a monoclonal antibody against ***S. aureus*** to prevent VAP in ICU patients in collaboration with Medimmune, a member of the AstraZeneca group. No other conflict of interest related to this manuscript to declare. Hasan Jafri is an employee of MedImmune, AstraZeneca, the manufacturer of anti-infectious disease monoclonal antibodies. He is currently leading the development and conduct of studies focused on prevention of nosocomial pneumonia, using monoclonal antibodies targeting ***S. aureus*** and ***P. aeruginosa***. No other conflict of interest related to this manuscript to declare. Marc Bonten is a member of the study team of an ongoing international phase II trial testing a monoclonal antibody against ***S. aureus*** to prevent VAP in ICU patients in collaboration with Medimmune, a member of the AstraZeneca group, as part of the IMI-funded COMBACTE and COMBACTE MAGNET projects. No other conflict of interest related to this manuscript to declare.

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