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Multidrug resistant (or antimicrobial-resistant) pathogens - alternatives to new antibiotics?

Brunel Anne-Sophie, Guery Benoit

Infectious Diseases Service, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Switzerland

Summary

For the last few decades, multidrug resistance has become an increasing concern for both Gram-positive and Gram-negative bacteria. The number of new molecules has dramatically decreased and antibiotic resistance is now a priority in the international community. Facing this new threat, a large number of new as well as "old" solutions are now being discussed in the medical community to propose an alternative to antibiotic treatments. A first option is to potentiate the effect of existing molecules through combinations to circumvent the individual molecule resistance. The second option is to neutralise either the infectious agent itself or its by-products using specific antibodies. A third option is to use the pathogen signaling mechanism and inhibit the production of virulence factor through quorum sensing inhibition. A fourth pathway would be to interact with the patient's microbiota using either probiotics or faecal transplantation to modulate the innate immune response and improve response to the infectious challenge, but also to act directly against colonisation by resistant bacteria by replacing the flora with susceptible strains. The last option is to target the bacteria using phage therapy. Phages are natural viruses that specifically infect target bacteria independently of any antibiotic-susceptibility profile. In this review, we will discuss each of these options and provide the scientific rationale and the available clinical data. In the majority of cases, these treatments represent an interesting approach but not the ultimate solution to multiresistance. Well-performed clinical trials are still missing and the major priority remains to promote good use and appropriate stewardship of antibiotics to decrease resistance.

Key words: *microbiota, phage, probiotics: quorum sensing*

Correspondence:
Benoît Guery, MD PhD, Service des Maladies Infectieuses, Département de Médecine, BH10-549, Rue du Bugnon 46, CH-1011 Lausanne, benoit.guery[at]chuv.ch

Introduction

With the appearance of penicillin, antibiotics became one of the most important revolutions in infectious-disease management. The medication was followed in subsequent decades by a growing number of new agents. The most obvious consequence was the rapid emergence of resistance associated with the use of each new agent. Today, the number of antiobiotic molecules is reaching a plateau, but resistance continues to grow. In 2013, the United States Centers for Disease Control (CDC) published a report outlining the top 18 drug-resistant threats to the USA. Among these, carbapenem-resistant *Enterobacteriaceae* were classified as urgent, and multidrug-resistant *Acinetobacter*, extended spectrum *Enterobacteriaceae*, vancomycin-resistant *Enterococcus* and multidrug-resistant *Pseudomonas aeruginosa* were qualified as serious threats. Recently, the European survey of carbapenamase-producing *Enterobacteriaceae* (EuSCAPE) performed a prospective multinational study on 2703 clinical isolates involving 455 sentinel hospitals in 36 countries [1] (85% *K. pneumoniae* and 15% *E. coli*). The results showed that 850/2301 (37%) *K. pneumoniae* and 77/402 (19%) *E. coli* were carbapenemase producers (KPC, NDM, OXA-48 like, or VIM). Similarly, for extended-spectrum beta-lactamase, a retrospective study over 5 years was performed in a French hospital and showed that incidence significantly increased from 5.2% of all positive *E. coli* blood cultures in 2005 to 13.5% in 2009 [2]. A meta-analysis studying faecal colonisation among healthy individuals included 66 studies on 28 909 healthy individuals, and showed a pooled prevalence of colonisation with extended-spectrum beta-lactamase producers reaching 14% with an annual-increase trend of 5.38% [3]. Finally, in a very elegant review, Bassetti et al. reported that colistin resistance could cause up to 10 million deaths per annum by 2050 and cost an excess of USD 100 trillion to the world's economy [4].

If antibiotic stewardship and good use is the logical answer to resistance, we are now facing infections with a limited number of therapeutic options, and alternative treatments must be developed. These options are either based on specific targets on the bacteria, or designed to improve the host response to the infectious injury. In this review we will discuss these therapeutic options and provide the scientific and clinical data available.

Combination of antibiotics

The spread of multidrug-resistant, extensively drug-resistant and pan-drug-resistant Gram-negative pathogens is causing an unprecedented public health crisis. *Pseudomonas aeruginosa, Acinetobacter baumanii,* and *Klebsiella pneumoniae* are the most common pathogens associated with multiresistance. Multidrug-resistant (MDR) Gram-negative bacilli (GNB) are resistant to antipseudomonal β-lactams, carbapenems, fluoroquinolones

and aminoglycosides, limiting therapeutic options in cases of serious infection that are seen most often in critically ill patients with comorbidities.

The non-negligible risk of inducing further resistance by the use of last-resort antibiotics and the limited current therapeutic options [5] led to the revival of two 'old' antibiotics 10 years ago: colistin [6, 7] and fosfomycine [8]. Intravenous colistin is a cationic peptide with bactericidal activity against *P. aeruginosa* and other GNB. Several studies have demonstrated *in vitro* synergy between colistin and β-lactams, rifampicin or fosfomycin against MDR GNB. Few case reports have documented the success of these salvage-treatment combinations containing colistin [7, 9–15]. Although the use of colistin monotherapy has been identified as a risk factor for the development of resistance during treatment [16], no clear survival benefit of combinations containing colistin over colistin monotherapy has been demonstrated [11, 17]. But a better infection outcome was observed in patients treated with colistin alone or colistin/meropenem than those receiving colistin in combination with other antibiotics [11]. For *A. baumanii*, no effect of the combinations colistin/rifampicin or colistin/fosfomycin on mortality has been shown in three randomised controlled trials (RCTs) [17]. Two RCTs are currently being performed to compare colistin alone with colistin/meropenem for the treatment of severe infections caused by carbapenem-resistant GNB [18].

Fosfomycin could also be a good therapeutic alternative for the treatment of MDR GNB infections due to its bactericidal activity and the absence of cross resistance with other antibiotics. Fosfomycin was synergistic *in vitro* in combination with β-lactams, colistin, aminoglycosides or tigecycline against MDR *P. aeruginosa* and CPE [8, 19], and effective in treating severe infections in association with these antibiotics in a few studies [8, 19–22]. However, only 30.2% of the MDR *P. aeruginosa* isolates were susceptible to fosfomycin, which limits the use of fosfomycin in empirical therapy [21].

Tigecycline is potent *in vitro* against MDR *A. baumanii* and CPE and has been utilised off-label in critically ill patients [5, 20]. Combination therapy and higher dosage are suggested due to disadvantageous pharmacokinetic parameters [5, 20] even though the level of evidence is low.

With the limitations of non-RCTs, combinations containing high-dose and prolonged infusion meropenem in order to prevent treatment failure have demonstrated a survival benefit in CPE infections if the minimum inhibitory concentration (MIC) is ≤8mg/l [23–25], and even if the MIC is ≥16mg/l [26] compared to other combinations, but with a close monitoring of optimal meropenem exposure [20].

New drugs for MDR *P. aeruginosa* (ceftazolane-tazobactam and ceftazidime-avibactam) and for selected carbapenemase-producing *Enterobacteriaceae* (CPE) (ceftazidime-avibactam) are already available. These new drugs are approved for complicated intra-abdominal infections and urinary tract infections. They are effective and produce minimal side effects. In a retrospective study including 35 patients with carbapenem-resistant *P. aeruginosa* infections, 87% of the isolates tested (n = 26/30) were susceptible to ceftazolane-tazobactam including 19 of the 23 isolates resistant to all other β-lactams. ceftazolane-tazobactam was successful in 26 patients (74%), mostly prescribed in monotherapy (77%), and failure was observed when isolates had MICs ≥8 μg/ml [27]. For CPE infections, the clinical experience of ceftazidime-avibactam is currently limited to case series [20, 28] with promising clinical results, but the question of monotherapy or combination remains unclear.

Novel antibiotic compounds targeting MDR GNB are under investigation, including meropenem-vaborbactam, imipenem-relebactam, plazomicin, cefiderocol and eravacycline [5, 20, 29]. Among these, meropenem-vaborbactam and plazomicin have already shown promising results.

The best available treatment against MDR GNB is unknown. Combinations seem attractive when looking at *in vitro* results or the lower mortality rates compared to monotherapy for the treatment of severe CPE in retrospective cohort studies [23–25, 30, 31], but these results are to be weighed cautiously and RCTs are urgently needed before a formal recommendation. Most of the data are derived from *in vitro* studies with limited *in vivo* translation [32], and from observational non-randomised studies with low-level evidence and high risk of bias. There is likewise no *in vivo* evidence that combination therapy prevents antibiotic resistance. Combination therapy may therefore be an option in CPE severe infections or, as an expert panel has proposed, in critically ill patients [5, 20] while keeping in mind the downside of the combination such as more side effects and the pending results of RCTs (NCT01597973 and [18]). For non-critically ill patients without severe infections, RCTs are needed to evaluate the benefits and costs of antibiotic combination, and impact on resistance induction.

If Gram-negative pathogens are a clear challenge, the management of multidrug-resistant *Enterococcus* infections is also complicated because of resistance to ampicillin and vancomycin, which are two of the traditionally most useful antibiotics. Linezolide and daptomycin represent interesting options. Linezolid, a bacteriostatic agent, is the only drug specifically approved by the Food and Drug Administration (FDA) for the treatment of vancomycin-resistant *Enterococcus* (VRE) bacteraemia. Daptomycin, a lipopeptide antibiotic with a rapid bactericidal concentration activity against enterococci, has also been an option. Three metaanalyses compared linezolid to daptomycin alone in the treatment of VRE bacteraemia, and all three suggested a survival benefit with the use of linezolid [33–35]. However, the methodology of the studies has been questioned [36, 37], with speicifc focus on the inadequate dose of daptomycin (<6 mg/kg/day) [35, 38]. Furthermore, a large retrospective cohort study of VRE bacteraemia showed that daptomycin was superior to linezolid, which was associated with higher microbiologic failure rates, higher 30-day mortality and more treatment failure [37]. In this study, daptomycin was even relatively under-dosed (6 mg/kg/day). Finally, Chuang et al., in a prospective cohort study, showed that linezolid conferred no survival benefit compared to high doses of daptomycin (≥9 mg/kg/day) [38], but that high doses of daptomycin was associated with lower mortality compared with low doses, as already described by Britt et al. [39].

The emergence of daptomycin-resistant strains during therapy with low doses of daptomycin monotherapy causing clinical failure [40] led to the use high doses of daptomycin [41–43], but also combination with other antibiotics [44]. Association with ampicillin could be interesting because

ampicillin can alter the surface charge of these strains by allowing the cationic daptomycin/calcium complex to bind more effectively to the cell wall [45]. Ceftaroline also has significant effects on growth rate *in vitro* as well as causing biophysical changes on the cell surface of VRE that can potentiate the activity of daptomycin and innate cationic host defense peptides, even if *Enterococci* are ceftaroline resistant [46]. *In vitro* synergy of daptomycin plus rifampicin or tigecycline has also been reported [43]. Nevertheless, only a few case reports have documented successful combinations of daptomycin with other antibiotics [44, 47] and these synergies observed *in vitro* have not been clinically validated by appropriate trials. Moreover, increased daptomycin use has recently been associated with resistance development in *E. faecium* bacteraemia over time even when combined with β-lactam antibiotic [48]. Clinicians should be aware of the risk of the emergence of daptomycin resistance and should monitor daptomycin MICs of *Enterococci* during treatment.

Despite the development of novel drugs with activity against VRE, such as oritavancin and tedizolid, the best therapeutic strategy to treat VRE bacteraemia remains to be established and randomized clinical trials including combination therapies are urgently needed.

Vancomycin is commonly used to treat serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Treatment failures have been described, most often in association with increased vancomycin MICs: vancomycin-intermediate *S. aureus* (VISA; MICs 4–8 μg/ml), heterogeneous VISA (hVISA; MICs in the susceptible range), or exceptionally VRSA (MICs >8 μg/ml). While the IDSA recommends monotherapy with vancomycin (level of evidence A, class of recommendation I) or daptomycin (level of evidence A, class of recommendation II) in cases of MRSA bacteraemia and endocarditis [49], evidence to suggest the need for rapid reduction of the bacterial inoculum and to prevent the emergence of resistance in combination therapy against these infections is growing.

Several studies have shown *in vitro* and *in vivo* the utility of the association of daptomycin and antistaphylococcal β-lactams, mainly oxacillin, in MRSA bacteraemia to enhance bacterial clearance. This is especially the case in daptomycin-non-susceptible strains (seesaw effect) [50], and prevents the emergence of daptomycin-resistant strains [51, 52]. The new cephalosporin, ceftaroline, is also interesting for its intrinsic activity against MRSA and its efficacy alone against daptomycin-non-susceptible strains *in vitro* and in animal models. The combination of daptomycin and ceftaroline was used successfully in salvage therapy after emergence of daptomycin-non-susceptible MRSA [53, 54], but also in a recent case of ceftaroline-resistant daptomycin-tolerant hVISA endocarditis [55].

Synergy *in vitro* between vancomycin and anti-staphylococcal β-lactams against MRSA, including oxacillin [56, 57], ceftaroline [57, 58], piperacillin-tazobactam [56] has been demonstrated recently even on hVISA or VISA, and the association between vancomycin and ceftaroline was used successfully to clear persistent daptomycin-non-susceptible MRSA bacteraemia [58].

There is limited experience of fosfomycin in combination with daptomycin, but some cases of MRSA bacteraemia or endocarditis have been successfully treated with this combination [59–61]. On the contrary, daptomycin in combination with rifampin or gentamicin has not been associated with a better response in an experimental model of MRSA endocarditis [62].

Although these results are *in vitro* data or case reports, a combination of antibiotics often seems effective for the treatment of serious MRSA infections. It is important to test all MICs to choose the best combination. In a pilot study by Davis et al. [63], combining flucloxacillin with vancomycin was able to shorten the duration of MRSA bacteraemia. Multicentre randomised controlled clinical trials are currently being performed to determine whether the combination of anti-staphylococcal penicillin plus standard therapy (vancomycin or high-dose daptomycin) [64] or high-dose daptomycin plus fosfomycin [59], result in improved clinical outcomes in MRSA infections.

In the era of multiresistance, combination of antibiotics is commonly used as salvage treatment to treat infections by extensively drug-resistant and pan-drug-resistant Gram-negative pathogens, but it is often sub-optimal [65]. Antibiotics are used off-label, at a higher dosage, and combined with more than two other antibiotics against a single pathogen, with proven synergy only *in vitro* [65]. Despite the results of observational studies, no RCTs have confirmed the advantage of combination therapy for the management of MDR infections. International collaboration is urgently needed to evaluate the survival benefit and the risk of resistance induction by performing RCTs to provide harmonised guidelines and ensure optimal use of our last therapeutic options available.

Antibodies

On 4 December 1890, Von Behring and Kitasato published the first paper using the blood of rabbits to neutralise tetanus and diphteria toxins [66]. Serum therapy was afterwards largely used in infectious diseases like pneumococcal pneumonia, meningococcal meningitis, dysenteria, or erysipelas [67]. This treatment was then abandoned for antimicrobial chemotherapy because administration of sera was associated with fever, allergic reactions and serum sickness. However, serum therapy persisted for a limited number of indications like hepatitis, measles, or toxin-induced diseases like tetanus, diphtheria and botulism.

If serum therapy was the first step, the improvement of the knowledge in immunology led to the development of specific antibody administration directed against a pathogen or a virulence factor. Two types of products are used. These are pooled polyclonal human immunoglobulins targeting several epitopes, or monoclonal antibodies focused on one specific target. However, administration of immunoglobulins or monoclonal antibodies does not stimulate the immune system so the effect does not persist over time.

Antibodies represent a classical approach in infectious diseases that is clearly not directly related to resistance. However, identifying determinants that are relatively conserved between strains, whether or not associated with virulence factors, could potentially be interesting in the context of multiresistance.

Antibodies in infectious diseases

Antibodies in sepsis

Facing multidrug resistance, an interesting approach could be to target the host's immune response, although this is of course specific to the type of resistance itself and the effect could therefore be limited in cases of total antibiotic resistance. Cytokines represent a normal response to infection but excessive production is associated with organ and tissue damage. For many decades sepsis was analysed as a hyperinflammatory syndrome, but more recently several authors have suggested that sepsis is a dynamic process that is both a pro-inflammatory state to anergy and immunoparalysis [68]. Immunotherapy has been largely explored in sepsis with a very large number of studies trying to block the effect of mediators or signaling molecules.

Many studies have evaluated the potential role of intravenous immunoglobulins in sepsis with a rationale based on the neutralisation of endotoxin, and immunomodulation with a reduced production of pro-inflammatory mediators and increased production of anti-inflammatory mediators. Two meta-analyses suggested that intravenous immunoglobulins reduced mortality in adults with sepsis [69, 70], but the more recent Cochrane analysis drew on 43 studies to show that this benefit disappeared when considering only the trials with low risk of bias [71]. Recently, in 2014, Cavazzuti et al. studied the influence of early therapy with IgM-enriched polyclonal immunoglobulin in septic shock and showed a 21.1% mortality reduction in the group that received IgM [72].

Another approach could be to target bacterial endotoxin. In 1991, Ziegler showed that HA-1A, a human monoclonal IgM antibody that binds to the lipid A domain of endotoxin, could decrease mortality in patients with Gram-negative bacteraemia and shock at entry [73]. These results were not confirmed in a second trial [74].

The first milestone in the potential role of cytokine inhibition was published in 1987. Tracey et al. showed that administration of neutralising monoclonal anti-tumor necrosis factor antibody administered to baboons before bacterial challenge protected against shock [75].

Based on this initial study, a number of clinical trials were carried out and showed no significant clinical benefit [76]. An interesting analysis was performed in 2005 by Lorente and Marshall. This underlines the major discrepancies between the studies and the models used to evaluate the effect. Global neutralisation of tumour necrosis factor-alpha (TNFα) is associated with the impairment of antimicrobial defenses [77].

Using the same initial rational, interleukin (IL)-1 inhibitor or antagonists of the IL-1 receptor led to comparable results. With a cohort of 893 patients with sepsis syndrome, recombinant human interleukin 1 receptor antagonist did not modify the survival time compared to the placebo [78], and a confirmatory study with 696 patients was published three years later [79]. Since these early studies, antagonising the activities of pro-inflammatory cytokines has failed to provide clinical benefit despite evidence to the contrary obtained from animal studies. In 2013, eritoran, a synthetic lipid A antagonist blocking lipopolysaccharide from binding at the TLR 4 receptor, failed to improve mortality at 28 days with no differences even in pre-specified subgroups [80]. One of the most promising pathway recently proposed is related to T-cell exhaustion observed in sepsis. Programmed cell death 1 (PD-1) is induced after T-cell activation. PD-1 is a negative co-stimulatory molecule linked to T-cell exhaustion in sepsis [81]. Brahmamdam et al. showed in a cecal ligation peritonitis model in mice that anti-PD-1 antibody prevented sepsis-induced depletion of lymphocytes, blocked apoptosis, and improved survival [82]. The clinical evaluation is yet to be performed. Other targets could also be proposed like the migration inhibitory factor (MIF) [83] or the high mobility box-1 (HMGB-1) [84] considered as late cytokines. One of the approaches discussed for the future would be to propose a tailored treatment targeting more than one cytokine based on the patient's profile (genetic polymorphism).

Globally all these new therapeutics and potential pathways to explore are of course interesting in the context of multi resistance where the host response is critical to the pathogen clearance. However, this is clearly not specific to resistance itself and actually developed for susceptible pathogens.

Virulence factors

Targeting virulence factors has been proposed for various bacteria, and a good example is *Staphylococcus aureus*. A chimerised monoclonal antibody against lipoteichoic acid protective in animal models for coagulase negative staphylococci and *Staphylococcus aureus* bacteraemia, it showed a good safety profile with good activity at 3 and 10 mg/kg in healthy adults [85]. A phase I/II double-blind placebo-controlled study evaluated the preventive effect of this molecule (pagibaximab) for staphylococcal bloodsteam infections in very low birth weight neonates [86]. The number of patients was not sufficient to reach a conclusion but the authors observed sustained plasma anti-lipoteichoic acid levels following the second dose [86]. A phase II study in the same population reached similar conclusions with a trend for efficacy but no definitive conclusions related to a small number of patients [87].

Tefizumab is a humanised monoclonal antibody that binds to the surface-expressed adhesion protein clumping factor A [88]. The development was stopped after a phase II randomised multicentre study where the molecule failed to show a major clinical effect [89]. Similarly, Altastaph, a polyclonal anti-*Staphylococcus aureus* capsular polysaccharide immunoglobulin showed only slight efficacy and was not further developed after two phase-II trials [90, 91]. Several other approaches are currently being explored that target the alpha-hemolysin, and the alpha-toxin conserved antigens, Luks-PV, or the Panton-Valentine leukocidin [92–96].

P. aeruginosa is a Gram-negative bacterium associated mainly with respiratory and urinary-tract infections. This pathogen is largely associated with ventilator-associated pneumonia with a high morbidity and mortality [97]. Another potential target is the apparatus associated with the production of virulence factor like the type-three secretion system (TTSS). *Pseudomonas* produces a large number of virulence factors [98] but TTSS is probably one of the most sophisticated systems [99–101]. A part of the TTSS, PcrV, belongs to the translocon allowing the secretion of four exotoxins: Exo U, S, T, and Y. In a seminal paper published in 1999, Sawa et al. showed the major role of PcrV in *Pseudomonas*-induced mortality [102]. These re-

sults were also confirmed in a different model [103]. The key role of the TTSS was also shown in *Pseudomonas aeruginosa* pneumonia-induced septic shock. TTSS toxins were associated with the decompartimentalisation of the inflammatory response [104]. Again other authors have shown comparable results [105, 106]. In 35 patients with *P. aeruginosa* pneumonia, Hauser et al. demonstrated that TTSS expression was associated with poor clinical outcome (81% of severe diseases with TTSS versus 38% without TTSS) [107]. A nice review summarises the knowledge between TTSS and clinical outcome [108]. With these data showing the clinical relevance of the TTSS, it seemed interesting to develop antibodies directed against the TTSS. A prospective randomised double-blind placebo- controlled trial evaluated an anti-PcrV PEGylated monoclonal antibody in mechanically ventilated patients colonised with *P. aeruginosa* [109]. The results showed a favorable tolerance profile and a reduction of *P. aeruginosa* pneumonia incidence. Although these results were interesting, there was no further development of this antibody.

Another opportunity for immunisation could in combination with an anti-infective. In a murine model of *P. aeruginosa* acute infection, Song et al. associated monoclonal antibodies with relevant antibiotics and showed a synergistic effect with an improvement in survival [110]. Against *Stenotrophomonas maltophilia*, additive and synergic effects were obtained by combining anti-efflux pumps antibodies and antibiotics [111].

Some authors also tried to develop bispecific antibodies with a monoclonal antibody specific to the target pathogen and cross-linked with a monoclonal antibody specific to the complement (to activate pathogen clearance). This was tested with interesting results on several pathogens such as *P. aeruginosa*, *B. anthracis*, and *S. aureus* [112–114].

In the fungal area, several antibodies have also been studied. Enfungumab is a genetically recombinant antibody against heat-shock protein 90 with good activity against *Candida* spp [115]. Heat-shock protein has also been reported in *Cryptococcus neoformans*. Nooney et al. showed that the combination of amphotericin and enfungumab were synergic on this pathogen [116]. A phase III study in invasive candidiasis was conducted on 117 patients, and a complete response was obtained in 48% of the patients in the amphotericin group and 84% in the group receiving amphotericin and enfungumab [117]. Mortality also decreased from 18% to 4%. However, in 2006, the Committee for Medicinal Products for Human Use (CHMP) recommended the refusal of the marketing authorisation for the product due to matters of quality and safety concerns. A variant was then proposed but was not effective (no intrinsic fungicidal activity, no synergy with amphotericin) [118].

Targeting virulence factors is an interesting pathway, but in most cases, the antibody is directed against only one determinant of virulence. For this reason, and for bacterial as well as fungal studies, the antibody is associated with an antibiotic or an antifungal, and killing the bacteria will remain a key issue – although blocking virulence may allow host response to be more efficient.

Quorum sensing

Quorum sensing is a signalling mechanism involving the exchange of chemical signals in bacterial populations to adjust the bacterial phenotype to the density of the population. The chemical signals are small molecules called autoinducers. The autoinducers diffuse freely or actively and reflect the density of the global population. When a threshold of concentration is reached, the gene expression program of the bacterial cells is altered and gene transcription is switched on or off. Autoinducers represent a large community of molecules including oligopeptides, like the autoinducing peptides of *S. aureus*, dihydroxypentanedione derivates like autoinducer-2 of *V. harveyi*, or acyl-homoserine lactones in Gram-negative bacteria [119]. In *S. aureus*, the expression of various virulence factors is regulated by the cell-density-dependent quorum-sensing accessory gene (agr) system. Short peptides are used as signalling molecules, and *S aureus* encodes four different allelic autoinducing peptide variants [120]. In *Staphylococcus* infection, quorum sensing regulates biofilm formation and toxin production. RNAIII inhibiting peptide has been shown to inhibit quorum sensing [121]. Recently Simonetti et al. evaluated the combined effect of quorum sensing inhibition with the administration of a new RNAIII inhibiting peptide derivative associated to tigecycline in a wound infection model [122]. Their results show that the combined effect induced a positive interaction *in vivo* in this model. Recently, myricetin, a flavonoid, was shown to decrease the production of several *S. aureus* virulence factors independently of the agr quorum sensing system, and could represent an interesting pathway [123].

Pseudomonas aeruginosa relies on three quorum-sensing systems: *las*, *rhl* and the *Pseudomonas* quinolone signal. *las* and *rhl* are based on the production of two acyl-homoserine lactones. These auto inducers control a large number of virulence factors including elastase, alkaline protease, exotoxin A, rhamnolipides, pyocyanin, lectins and biofilm [124]. The clinical relevance of the inhibition of the quorum sensing system has been demonstrated even with clinical strains [125]. A large number of compounds have shown potential and could be used to inhibit quorum sensing like furanones, antibiotics, plant extracts, garlic, and synthetic inhibitors [126–130].

Besides *S. aureus* and *Pseudomonas aeruginosa*, quorum sensing has been described as a regulator of virulence for other pathogens like *E. coli*, *Salmonella* or *Francisella tularensis* [119] and is considered as a relevant target to combat bacterial virulence.

Inhibition of the quorum sensing is neither bacteriostatic nor bactericidal, but should decrease virulence. It must therefore be emphasised that this approach is an adjunctive treatment to antibiotics. Even if the concept is now widely accepted, the number of studies in humans remains very limited. Azithromycin has been extensively studied *in vitro*, in animal models, and some data have been obtained in humans. It was shown that this molecule could block neutrophil recruitment in *Pseudomonas* endobronchial infection in mice [131], block quorum sensing-regulated virulence factor in a chronic model [127], and increase survival in CF mice [132]. However, the clinical data are not conclusive. In ventilator-associated pneumonia, no study showed a difference in mortality [133–135]. Azithromycin

has also been proposed in cystic fibrosis [136] and COPD [137]. Although the rationale seems interesting and some data promising, we still need a well-conducted study to find the place of quorum sensing inhibition in the era of multiresistance.

Bacteriocins

Bacteriocins are antimicrobial peptides produced by bacteria. Bacteriocins are small peptides and include ribosomal or non-ribosomal compounds. They represent a heterogenous group classified into peptides that undergo post-translational modifications versus unmodified peptides [138]. These molecules present a low toxicity and can have a wide spectrum. They are usually cationic amphiphiles, and unstable (susceptibility to proteases). Among all the molecules, only magainin was submitted to the Food and Drug Administration, but was rejected and no other molecules are currently proposed for humans [139]. In the future, brilacidin is one of the lead components developed from a series of small molecules with potent activity on a broad range of drug-susceptible and multidrug resistant Gram positive and negative bacteria. Mensa et al. showed that Brilacidin could cause membrane depolarisation to an extent comparable to daptomycin [140]. Other molecules were evaluated such as thuricin, a narrow spectrum bacteriocin active against *Clostridium difficile* [141]. *In vitro* data suggest a potentially interesting effect as a targeted therapy in *C. difficile* infection. A role on biofilm formation was also demonstrated [142].

These molecules could potentially be very interesting in the context of multiresistance based on their broad spectrum and lasting effect even on multiresistant strains. Bacteriocins are also bactericidal and target Gram-positive as well as negative pathogens. To date, there is no molecule available for patients, and well-designed clinical trials are needed.

Probiotics

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit to the host [143]. The probiotics used are strains of bacteria, usually *Lactobacillus* or *Bifidobacterium,* both of which are part of the normal gut microbiota, and fungi such as *Saccharomyces boulardii*. Most are marketed as fermented foods or dairy products or dietary supplements, which can explain the absence of minimal manufacturing standards with regulatory oversight as well as the lack of studies demonstrating health benefits or potential mechanism(s) of action. Nonetheless, probiotics are used to prevent and/or treat a wide range of diseases and conditions that affect humans and animals.

Mechanisms for the benefits of probiotics are still incompletely understood. It is generally presumed that the molecular mechanisms of probiotics are triggered by so-called bacterial-epithelial "cross talk". The activation of the transcription factor nuclear factor κB (NFκB) induces the synthesis of inflammatory cytokines, the basis of an acute innate inflammatory response. The probiotics have been shown to interact through four main pathways [144]:

− Antimicrobial activity with the suppression of growth or expression of bacterial virulence factors. Probiotics produce both acids that lower the pH of the local environment, and toxins inhibiting the growth of other bacteria [145], such as *Clostridium difficile.*

− Prevention of gastrointestinal tract colonisation by pathogens: most probiotics temporarily colonise the gut, producing bactericidal acids and peptides, which promote "competition" between the probiotic and pathogens such as *C. difficile* [146].

− Modulation of the host immune system: probiotics modulate innate and adaptative immune systems by stimulating toll-like receptors and up-regulating cytokine expression in dendritic cells and peripheral blood monocytes. So, the effects of probiotics on the development of host defense are generalised mucosal immune response, balanced T-helper cell response, self-limited inflammatory response, and polymeric IgA secretion [144].

− Improvement of gastrointestinal barrier integrity: *Lactobacillus* strains up-regulate mucous genes in intestinal goblet cells leading to the activation and the secretion of mucus in the intestine responsible for the inhibition of pathogenic bacteria attachment to the mucosal barrier [144].

When it comes to potential adverse effects, Lactobacilli, Lactococci and *Bifidobacterium* are classified as "generally regarded as safe" [143] based on the long history of extensive use by millions of individuals and limited side effects described [147]. Bacteraemia, endocarditis and liver abscess have been reportedly caused by *Lactobacillus spp.* in patients with central venous catheters, intestinal feeding tubes and/or severe comorbidities [147], as well as *S. boulardii* fungaemia [148]. Many controlled clinical trials demonstrate that the use of probiotics is safe without evidence of toxicity (mainly for *Lactobacillus*) in certain at-risk populations, such as pregnant women, premature neonates, elderly or critically ill individuals [147]. Nonetheless, the lack of safety data for certain probiotics in vulnerable patients calls for cautious use in these members of the population. Other concerns about toxicity to the gastrointestinal tract, precipitating lactic acidosis and/or transfer of antibiotic resistance, remains theoretical without data reports [147].

In the light of these data, we can wonder what would be the place of probiotics for the prevention and the treatment of MDR bacteria. Machairas et al. have shown that intraperitoneal pre-treatment with probiotics (*Lactobacillus*, *Saccharomyces* and *Bifidobacterium*) significantly prolonged survival after experimental infection with MDR *Pseudomonas aeruginosa* in mice (66.7% vs 31.3%; p = 0.026) by having an effect on sepsis-induced immunosuppression (TNFα and IL-10 productions increased, interferon-gamma production decreased, IL-17 production restored) [149]. One of the major problems regarding antibiotic resistance is the capacity of MDR Gram-negative bacilli (GNB) or vancomycin-resistant *Enterococcus* (VRE) to colonise the gastrointestinal tract of patients for many months [150], which constitutes a reservoir of MDR bacteria in hospitals and the community. Moreover, the risk of infection with MDR bacteria increases in colonised patients with these bacteria. Thus, one of the strategies of prevention could be to use probiotics in patients harboring MDR bacteria for the decolonisation of the gastrointestinal tract. In the only randomised double-blind placebo-controlled clinical trial to date, probiotics were not ef-

fective for decolonising hospitalised patients harbouring MDR GNB [151]. Clinical trials have also been performed for VRE, but interestingly showed the efficacy of *Lactobacillus rhamnosus* GG in eradicating VRE carriage [152, 153]. Similarly, probiotics could have a place in the prevention of methicillin-resistant *Staphylococcus aureus* infections (MRSA) in eliminating this pathogen from the nasal cavity. Indeed, it is known that *S. aureus* nasal carriers are three times more at risk of developing nosocomial bacteraemia than in non-carriers [154] and that *S. aureus* carriage eradication by mupirocin is partially efficient with the possibility of the acquisition of mupirocin resistance. Non-clinical studies showed that many strains of lactobacilli and bifidobacteria inhibited the growth of *S. aureus* and clinical isolates of MRSA *in vitro* [155]. However, very little data exist for the clinical use of oral and/or nasal probiotics in patients with MRSA colonisation. Three prospective studies showed the elimination of MRSA colonisation with probiotic use with a decreased incidence of MRSA infections for one of them [155].

Therefore, probiotics could be important mainly for the prevention of MDR bacteria infections by modulating the host immune response, especially in the case of VRE or MRSA carriage. But clinical trials are needed to evaluate the efficacy of probiotics for the treatment of MDR infections.

Faecal microbiota transplantation (FMT)

The gut microbiota is a major player in the host immune response to infection, modulating first-line immune players as well as local and remote response to injury. The role of faecal microbiota transplantation has already been demonstrated in *Clostridium difficile* infection (and specifically recurrent infections) [156, 157] and this treatment belongs to the European guidelines for recurrent *Clostridium difficile* infection [158]. Interestingly, FMT has also been proposed in other diseases like inflammatory bowel diseases [159–161], diabetes [162], or obesity [163].

The gut microbiota influences the neutrophilic response to diverse stimuli. Karmarkar et al. evaluated neutrophilic response after an intraperitoneal (i.p.) injection of zymosan, silica or monosodium urate in germ free or flora-deficient mice [164]. Their results showed impaired blood extravasation of neutrophils in flora-deficient mice. Neutrophil recruitment required stimulation by microbiota of a myeloid differentiation primary response gene-88-dependent pathway (MyD88 is an adaptor molecule of most Toll-like receptors). In a model of infection by *Escherichia coli*, Balmer et al. showed that Toll-like receptor (TLR) signaling was essential for microbiota-driven myelopoiesis [165]. In a neonatal mouse model, antibiotic exposure attenuated post-natal granulocytosis by reducing IL-17 producing cells in the intestine. This relative granulocytopenia increased the susceptibility of mice to *E. coli* and *Klebsiella pneumoniae* sepsis [166].

Locally, gut microbiota participates tresistance to intestinal pathogens. Ivanov et al. showed that colonisation of the small intestine with segmented filamentous bacteria (sfb) increased the frequency of CD4+ T-Helper by producing IL-17 and IL-22 in the lamina propria [167]. This colonisation also enhanced resistance to *Citrobacter rodentium* infection.

The gut microbiota influence the response to injury of remote organs, notably the lung. A seminal work published in 2011 evaluated the response to respiratory Influenza virus of mice subjected to 4 weeks' oral administration of a combination of antibiotics (vancomycin, metronidazole, neomycin and ampicillin) [168]. Influenza-virus-specific antibody titres and CD4 T-cell responses were significantly reduced, while lung viral titer remained significantly elevated in antibiotic-treated mice. Consistent with this first study, Fagundes et al. showed that germ-free mice are extremely susceptible to an intratracheal challenge of *K. pneumoniae* [169]. Priming of mice with TLR agonists restored their resistance to pulmonary infection. These results show that gut colonisation enables an adapted inflammatory response. Similarly, Gauguet et al. showed that mice lacking intestinal sfb developed a more severe pneumonia than mice colonised with sfb when animals were challenged intranasally with methicillin-resistant *Staphylococcus aureus* [170]. In this model, the presence of sfb promoted pulmonary type 17 immunity and resistance to *S. aureus* pneumonia, and exogenous IL-22 protected mice deficient in sfb from *S. aureus* pneumonia. Using mice depleted or not of gut microbiota with antibiotics and subsequently infected intranasally with *Streptococcus pneumoniae*, Schuijt et al. showed that the gut microbiota protected against bacterial dissemination, inflammation, organ damage and mortality [171]. The protective phenotype conferred by the microbiota was related to enhanced phagocytosis and cytokine response to lipotechoic acid and lipopolysaccharide by alveolar macrophages from control mice when compared to microbiota-depleted mice. Altogether, these results suggest a major role of the "gut-lung" axis and another way to look at the lung response and potential therapeutic innovative pathways.

In multiresistance, FMT has also been proposed to eradicate colonising antibiotic-resistant bacteria. Bilinski et al. performed 25 FMT in 20 patients colonised by a median of 2 strains of antibiotic-resistant bacteria [172]. Decolonisation at 1 month was obtained in 60% of the cases, suggesting that FMT was safe and efficient to eradicate antibiotic-resistant bacteria in the subpopulation of patients with blood disorders included in this study. 10 studies are currently listed on clinicaltrial.gov that are designed to evaluate FMT in gut colonisation with antibiotic-resistant bacteria.

FMT and all the potential alternatives with synthetic microbiota could represent an attractive solution for antibiotic-resistant bacteria colonisation, but it must be remembered that we only evaluate this short-term endpoint. In fact, it seems that FMT could clear antibiotic-resistant bacteria colonisation earlier than the normal evolution (but other studies also need to confirm this finding). Several studies have also shown that gut microbiota was a major factor associated with the modulation of the host immune response [173], so any manipulation of the gut microbiota could potentially be associated with long-term consequences that we must at least monitor in this subgroup of patients where the vital prognosis is not engaged.

Phage therapy

Among the potential strategies that could be developed facing multidrug resistance, phage therapy is one of the

most promising approaches. This "forgotten cure" uses natural viruses present in all ecosystems that infect specific bacteria and are unable to infect eukaryote cells.

Discovered in 1915 before penicillin [174], the bacteriophage therapy era began after its first use in 1917 by Felix d'Herelle [175] and is still commonly used in Eastern European countries. The lack of data on pharmacokinetics/pharmacodynamics, immunological response, *in vivo* efficacy, and emergence of resistance were potential reasons why this treatment was not developed on a large scale in other countries a century later.

With a size of 25–200 nm, phages behave like other viruses with mainly two types of replication cycles: lytic cycle and lysogenic cycle. The phage penetrates into the bacteria after attachment then viral nucleic acid (mainly DNA) is released into the bacterial cytoplasm. During the lytic cycle, the virus uses the host cell's metabolic machinery to make large amounts of viral components, and kills bacteria by cellular lysis thanks to phage endolysins, which allow the release of progeny virions to infect other bacteria [176–178]. Temperate phages undergo a lysogenic cycle during which the viral DNA is quickly integrated into the bacterial genome or remains in the form of plasmid, and is then duplicated along with all its genetic material during cell division. This new form of viral DNA in dormancy, called "prophage", can confer specific phenotypic advantages to the target bacteria, such as resistance or virulence [176–178]. For these reasons temperate phages are not considered in phage therapy.

Thus, the development of phage therapy is a promising way to improve the treatment of MDR bacteria. Independently of the administration route (local or systemic), phages behave as an exponential self-amplifying drug with *in situ* increasing concentrations in time. Indeed, the success of phage therapy in acute infections is determined not only by the type of phages and bacteria involved, but also by the bacterial density at the time of application and the proliferation kinetic. The timing of treatment is less crucial in chronic infections where bacteria are abundant. Moreover, beyond their potential efficiency on MDR bacteria, the impact of phages on the host gut microbiota is insignificant and the antibiotic selection pressure is null thanks to the narrow specificity towards the bacterial targets and their mode of action [177]. But this host specificity might also be a limitation with a risk of treatment failure if the target is not the bacterium responsible for the infection. So "broad-spectrum" phages or cocktails containing several phages targeting different strains of the same pathogen and/or different bacterial species were mostly used in therapeutics to increase antimicrobial activity and decrease the risk of phage-resistance development. Finally, one of the interesting properties of phages is their capacity to hydrolyse bacterial polysaccharides forming the biofilm [179]. While antibiotics penetrate with difficulty into biofilms, phage therapy could therefore play a role for the treatment of medical devices [178] or diabetic foot infections, or in cystic fibrosis patients [180], where disease is often caused by pathogens that are able to produce biofilm (*S. aureus* or *P. aeruginosa)*.

Efficacy and safety studies in animals have been performed during the last 20 years and demonstrate most often the efficacy of phages in different types of infections, including pneumonia [181–183], peritonitis, burns, chronic otitis, orthopaedic implant-related infection [184], bacteraemia [185] and more recently endocarditis [186], but also in the prevention of biofilm production, with different animal models and several bacteria/phage combinations [185, 186]. In humans, potential applications of phages are both phage-mediated prevention and phage treatment ranging from conventional phage therapy, to treatments with phage enzymes (e.g., endolysins) or combinations of phages with antibiotics. In theory, most bacterial infections could be treated by phage therapy, with the exception of strictly intracellular bacteria (no penetration into eukaryote cells), infections of the central nervous system, and polymicrobial infections [177]. While several clinical trials have evaluated the safety of phage therapy in humans for the treatment of venous leg ulcers [187] or diarrhoeal illness [188, 189], only a few studies have evaluated its efficacy. Topical phage therapy was used for the treatment of antibiotic-resistant *Pseudomonas aeruginosa* chronic otitis, a difficult-to-treat infection due to biofilm production. In a prospective randomised double-blind phase I/II trial, phage therapy improved clinical outcomes significantly and reduced bacterial counts without side effects [190]. In a randomised study evaluating oral phage therapy in enterotoxigenic and enteropathogenic *E. coli* – diarrhoea *versus* placebo in 120 children in Bangladesh, oral coliphages were safe but did not improve diarrhoea outcome, possibly due to the insufficient phage coverage and low phage doses [189]. Likewise, a recent case report showed the efficiency of bacteriophage monotherapy in the treatment of colistin-only sensitive *P. aeruginosa* bacteraemia in a patient with acute kidney injury [191]. Several multicentre, randomised controlled phase I/II trials of phage therapy are currently being held for the treatment of wound infections by *E. coli* and *P. aeruginosa* in burned patients (PHAGOBURN), in *S. epidermidis* and *S. aureus* bone and joints infections (PHOSA) or *S. aureus* diabetic foot ulcers infected (PHAGOPIED).

Bacteriophage resistance can appear by various mechanisms [192] during treatment, but the clinical impact is still not well studied [177].

Finally, understanding the interaction between bacteriophages and host immunity is essential for the rational use of this treatment. No tolerance issue was observed in previous studies when the preparation of phages, which were rich in bacterial degradation products and strongly immunogenic, were cleansed. Adaptative immunity can also be involved in the clearance of phages via the production of specific neutralising antiphage antibodies [193], induced by the phages themselves, but without consequences for the efficacy of phage therapy and the outcome of infections [194, 195].

Thus, phage therapy is not a universal therapeutic weapon but a future major ally against MDR bacteria that requires more research, as concluded by N. Dufour and L. Debarbieux in their review of phage therapy [177]. Phage therapy could potentially be very interesting in the context of multi resistance based on their broad spectrum, their *in situ* increasing concentrations in time, and their capacity to treat biofilm-related infections. To date, there are currently no phage applications for humans approved in the world, but phage therapy could be a safe alternative or association to antibiotic therapy [186, 196] in the context of MDR, and clinical trials are needed.

Table 1: Advantages and limitations of non-antibiotic approaches.

Target	Approach	Advantages	Limitations
Bacteria	Combination	Circumvent resistance mechanisms Revival of old molecules	Cumulated toxicity Difficulty to build randomised trial Evolution of resistance
	New drugs	Adapted spectrum	Limited number Cost
	Antibodies against virulence factors	Targeted therapy	Specific to a single factor/pathogen Requires diagnostic specificity Cost
	Quorum sensing inhibition	Focused on virulence factors	Lack of strong clinical proof
	Bacteriocins	Direct action on the bacteria Low probability of resistance	No clinical trial Pharmacokinetic/-dynamic parameters unknown
	Phage therapy	Specific of the bacteria Preservation of the microbiota Can be used topically	Catalogue of phage available Cost Mimited number of clinical proof Pharmacokinetic/-dynamic parameters unknown Requires diagnostic specificity
Host response	Antibodies in sepsis	Targeted therapy Not pathogen specific	Production Cost Not directly related to resistance A lot of failure in the past
	Probiotics	Available Cost	No clinical trial
	Faecal microbiota transplantation	Cost	Long term effect Limited number of clinical proof

Conclusion

In this review, we have presented several potential treatments that could be proposed in the case of multiresistant pathogens (table 1). Antibiotic combination will probably remain a valid option for a limited time. The fact that bacterial plasticity evolves under pressure is largely beyond our control. Similarly for antibodies, the window of opportunity in quite narrow and the potential for bacteria to associate different virulence mechanisms make the task of proposing a unique target very difficult. Manipulation of the microbiota is a real option but stands more in the preventive than curative area, and the long-term consequences constitute a major threat in the context of resistance. Finally, phages are a really attractive therapy but require an important infrastructure. Globally we have numerous different pathways but all of them still need well-constructed prospective studies, which are nowadays difficult to achieve. A lot of things can be done without new drugs, but the best path is to avoid the emergence of resistance and preserve our new as well as our old molecules.

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