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Review

Recent Progress in Phage Therapy for Controlling Multidrug-Resistant *Acinetobacter Baumannii* Including in Human and Poultry

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Abstract: *Acinetobacter baumannii* is a multidrug-resistant and invasive pathogen associated with the etiopathology of both an increasing number of nosocomial infections and of relevance to poultry production systems. Multidrug-resistant *Acinetobacter baumannii* has been reported in connection to severe challenges to clinical treatment, mostly due to an increase rate of resistance to carbapenems. Amid the possible strategies aiming to reduce the insurgence of antimicrobial resistance, phage therapy has gained particular importance for the treatment of bacterial infections. This review summarises the different phage-therapy approaches currently in use for multiple-drug resistant *Acinetobacter baumannii*, including single phage therapy, phage cocktails, phage -antibiotic combination therapy, phage coding *Acinetobacter baumannii* and the novel phage enzyme treatment. Although phage therapy represents a potential treatment solution for multidrug-resistant *Acinetobacter baumannii*, further research is needed to unravel some unanswered questions especially in regard to its *in vivo* applications, before possible routine clinical use.

Keywords: Multidrug-resistant *Acinetobacter baumannii*; Phage therapy

1. Introduction

The Gram-negative aerobic, non-motile, pleomorphic bacillus *Acinetobacter baumannii* [1] is a multidrug-resistant opportunistic pathogen, currently identified as one of the major causes of nosocomial infections in the healthcare system worldwide [2] . Moubareck et al. defined *A. baumannii* as the main causative agent of pneumonia, sepsis, meningitis, urinary tract and wound infections [3], correlated to a nosocomial mortality rate of up to 35% [4]. Antimicrobial resistance (AMR) has been identified as a major worldwide health threat; in recent years, the irrational use of antibiotics, especially broad-spectrum approaches, has led to an increased selection of microbial species able to both survive medical treatments and lead to an increased genomic distribution of AMR genes [5; 6]. Amongst the increasing number of multidrug-resistant bacteria reported, *A. baumannii*, especially nosocomial-relevant, has also been correlated to an increased resistance to multiple antibiotics [7]. Different outcomes have been reported for *A. baumannii* infected patients, including the need for cardiac surgery, with a prevalence of high-mortality pulmonary infections [8]. According to Asif *et al.* (2018), *A. baumannii* AMR gene distribution significantly differs between patients in different hospitals and departments [9]**.** Specifically, *A. baumannii* has been found resistant to common antibiotics, such as cefoperazone/sulbactam, ampicillin/sulbactam and piperacillin/tazobactam, while polymyxin B

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still showed strong antibacterial activity against multidrug resistant *A. baumannii in vitro* [10]**.** *A. baumannii* infection and drug resistance rates are generally increasing leading to a decrease effectiveness of general antibiotic therapy in worldwide. For example, carbapenems are critically important broad-spectrum antibiotics, whose pivotal therapeutical role is endangered by the insurgence of multi-resistance amongst multidrug resistant *A. baumannii* [6]. There is increasing evidence that extensively drug-resistant (XDR) and pan-drug-resistant (PDR) *A. baumannii* strains accumulate in, amongst others, countries like Iran and Croatia [11; 12; 13].

Poultry production has an essential contribution in food security and nutrition, with a fast-growing market [14], mostly due to poultry meat and eggs a rather affordable protein source [15]. A good number of regulations have led to a decreased usage of antimicrobial through food animal production [16], however *A. baumannii* is commonly found in poultry and their produce. Indeed, its role in as zoonotic AMR agent has been investigated [17] , indicating possible AMR transmission from poultry to humans [18]. Multidrug resistant *A. baumannii* has been listed as a key priority by the World Health Organization (WHO) in the attempt of identifying pathogens that pose an increased threat to human health [19], hence the urgent need for alternative treatment strategies.

Bacteriophages (phages) are viruses that specifically target bacteria with a basic structure constituted by an outer protein capsid enclosing the nucleic acid [20]. Similarly to other viruses, a typical phage lytic infection cycle is characterized by adhesion to the bacterial cell via recognizing host outer receptors, injection of phage genome into the cytosol, viral replication, followed by bacterial lysis and liberation of new phage [21]**,** which could potentially infect new susceptible bacterial cells. Phage therapy, based on such lytic dynamics, could function as self-amplifying "drug", targeting sensitive bacterial cells and therefore providing an alternative to antibiotic therapy [22]. Strictly lytic phages are usually preferred for phage therapy, whereas the use of temperate phages has been avoided due to their ability to mediate gene transfer between bacteria through specialized transduction, which may increase bacterial virulence [23] or horizontal AMR gene transfer [24]. Beyond being a promising alterative to classic antibiotics, aiming to decrease the insurgence of AMR, phages could be also used towards biofilms, whilst having lower systemic toxicity and improved self-reproduction abilities compared to classic antibiotics [25; 26]. Phage therapy has been relatively poorly studied in the past, in contrast the majority of the studies have focused their attention on classic antibiotics, targeting tolerance, immune response, pharmacokinetics, pharmacodynamics, and animal models of infection [27]. Recently, a significant number of studies on phage therapy have been published, underlining the important role of this possible therapeutical alternative [28; 29; 30; 31; 32] and in 2017, phage therapy was reported for the first time as possible treatment for *A. baumannii* infection [33]. The current state of the art in regard to both advantages and limitation connected with phage therapy is summarized in Table 1.

Research on bacteriophage as antibiotic alternative has become increasingly popular due to raise of AMR and the increasing number of multi-drug-resistant bacteria. Numerous *in vivo* and *in vitro* studies using single or mixed phage types (phage cocktails) have been conducted over the years. The following sections describe in detail the most common phage therapies tested so far, especially considering their applications against *A. baumannii* in both human medicine and applied to poultry production, including single phage therapy [47], phage-cocktails [48], phage-antibiotic combination therapy [49], phage-derived enzymes [50] and novel approaches to phage therapy, such as combination with photosensitisers [51](Fig. 1)

Table **1.** Advantages and limitations of phage therapy in comparison to antibiotics

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Advantage	Limitations
Narrow antimicrobial spectrum [34]	There is no definite optimal dosage and/or administration plan. Adaptive anti-phage immunity may develop through Multiple dosing may be connected to [35]
Abundant in water, soil and other ecological environment [36]	Technical challenges accompany the preparation of phagocytic mixture in advance [37]
Lower side-effects [38]	Can promote horizontal gene transfer through transduction, which may lead to the spread of drug resistance [39]
Low environmental impact [34]	Lack of reproducibility amongst results from different *in vivo* and *in vitro* studies [40]
Low impact on the broad microbial communities [41]	The immune response of the body may affect phage activity [42]
Low phage characterisation and isolation cost[43]	Stability and shelf life [44]
Effectiveness against bacterial biofilms [45]	Convoluted rational design (pharmacodynamics/pharmacokinetics) [46]

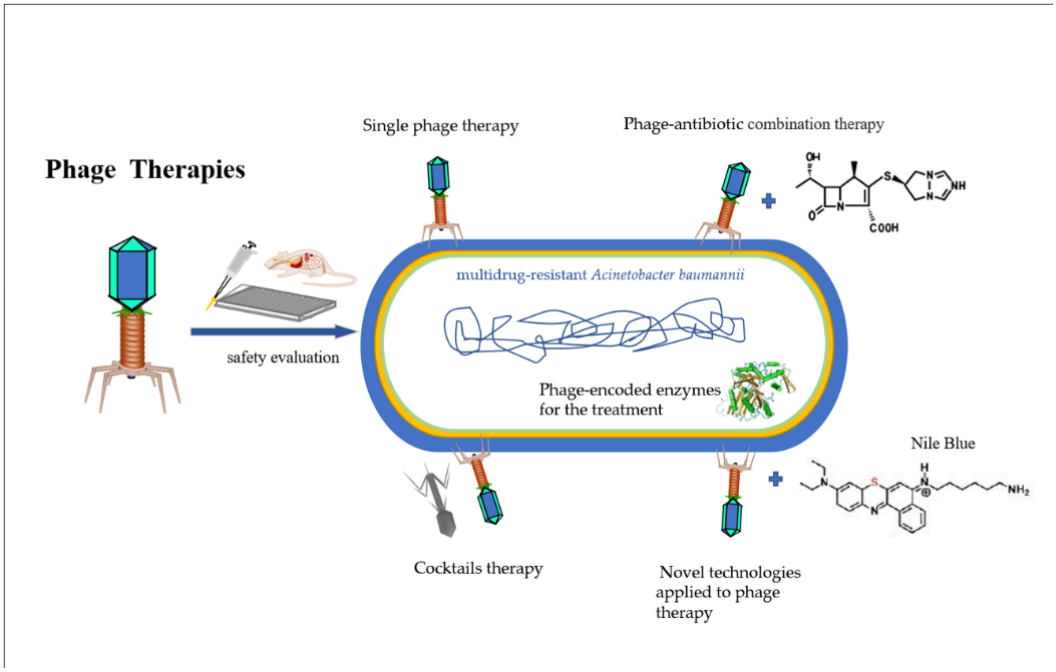

Figure 1. The most common phage therapies tested so far against pathogens, including single phage therapy, phage-cocktails, phage-antibiotic combination therapy,

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phage-encoded enzymes and novel applied to phage therapy, such as combination with photo-sensitisers.

2. Phage Therapy on human infection

2.1. Single phage therapy

Therapies based on a single virus type, also known as monophage therapies have been vastly applied as *A. baumannii* treatment. Jeonet *et al*. (2012) found that the phage YMC 13/03/R2096 ABABBP or the molar φ-R2096 exhibited high lytic activity against *A. baumannii* growth in a dose-dependent manner [52]. In another study, intranasally administered phage SH-AB15519, originally isolated from hospital wastewater, has been found effective in treating pneumonia led by carbapenem-resistant *A. baumannii* infection in mice [53]. Interestingly, phage SH-AB15519 has been demonstrated to be lacking genes connected to further virulence or AMR [22], possibly a symptom of its low integration rate, which might endorse the use of this phage as a possible antibiotic alternative. PD-6A3 is a novel *A. baumannii* phage, also inhibiting *Escherichia coli* and Methicillin-resistant bacteria [54]. Furthermore, Phage Abp9 effectively treated the biofilm produced by *A. baumannii* strain ABZY9 *in vitro* and contributed to positive treatment output in a murine model of *A. baumannii* infection [55]. Phage φ KM18P was used in XDR *A. baumannii* bacteraemia models in BALB/ C and C57BL/6 mice, where improved the survival rate of animals and reduced the number of bacteria in the blood, concurring with decreased levels of TNF- α and interleukin-6 [56]. The bacteriophage vB_AbaP_AGC01, isolated from a fish pond sample collected in Stargard (Poland), has been shown to have high specificity to *A. baumannii* and to generate high-yield viral offspring (317±20 plaque-forming units per cell) [57]. .Phage vB_AbaP_AGC01 alone or in combination with antibiotics (gentamicin , ciprofloxacin and meropenem) significantly reduced *A. baumannii* cell count in a human heat-inactivated plasma model [57]. In parallel, phage vB_AbaM_PhT2 prevented *A. baumannii* induced cell damage in human brain and bladder cell lines by significantly reducing the bacterial cytotoxicity and the dose of colistin needed [58]. Therefore, these findings could suggest that many phages in general, and perhaps phage vB_AbaM_PhT2 in particular, could be applied as an antibacterial agent in a hospital environment. Bacteriophage STP4-A screened by Mengzhe Li *et al*. has a strong inhibitory effect on both single and multiple *salmonella* strains and is a safe antibacterial agent with a wide host range, which can be used in the poultry industry. Tawakol *et al*.[59] showed that phage therapy (via intratracheal inoculation) not only reduced the severity of APEC infection when studied as a single pathogen infection, but also prevented mortality from co-infection of APEC and infectious bronchitis virus (IBV). In addition, phage treatment significantly reduced the number of pathogenic exfoliated *E. coli* and IBV in the mixed infection group but not in the case of IBV only challenge.

2.2. Cocktail therapy

Phage cocktails typically consist of multiple phages combined, each of them having unique host specificity due to selective affinity towards a specific bacterial receptor, conferring a broad therapeutically pyrolysis spectrum [60]. On the other hand, the development of phage resistance, especially to lytic viruses should be carefully monitored, and cocktails seem to be a valid approach to limit such occurrences. It has been shown, for example that a designed cocktail of phage vB_AbaS_D0, isolated from hospital-sewage samples in Dalian (China), and vB_AbaP_D2 decreased the mutation frequency of *A.*

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baumannii whilst also decreased the percentage of phage-resistance in a murine bacteraemia model [61]. Wu *et al*. reported the administration of a phage cocktail to four patients in a COVID-19 intensive care unit in China was able to treat carbapenem-resistant *A. baumannii* infection, otherwise showing the insurgence of phage-resistant *A. baumannii* strains when only one phage was administered [62]. The application of a cocktail of bacteriophages has also been demonstrated to be an effective substitute to antibiotic growth promoter replacement in broiler diets [63], which would further assist to reduce development of anti-microbial resistance arising from poultry production. The combination of phages (φkm18p, φTZ1 and φ314) as a cocktail was able to decrease the concentration of *A baumannii* in another study in contrast to single-phage administration, otherwise correlated to recidivist bacterial growth [64]. In parallel, another study demonstrated the improved output when using phage cocktail compared to single phage in lysing *A. baumannii* bacteria without further leading to resistance [65].

Similarly, the emergence of anti-phage mutants can be suppressed by ensuring a high titre throughout cocktail treatment. Beyond phage-resistance, another factor to consider is that treatment with high-populated phage cocktails may lead to complex pharmacological and immune responses, which may hinder the implementation of clinical trials [66], hence the recommendation of the use of a less complex cocktail consisting of up to 2-10 phages as the first choice [67]. As observed in other fields, the misuse of antibiotics associated with livestock including poultry production, has led to the selection and spread of multi-drug resistant organisms (MDRO), including *A. baumannii* [68]. The zoonosis risk associated with these MDRO is not only clinically relevant towards the development of a specific symptomatology, but it could also contribute to the spread of AMR to humans, thanks to mechanisms like e.g., horizontal gene transfer. Although the use of phage therapy to control *A. baumannii* infection in poultry has not been reported, many studies have been carried out on other pathogens in farming animals. Indeed, *Campylobacter jejuni* abundance in broilers was decreased by oral treatment with *Campylobacter*-specific- phage cocktail, without further affecting microbiota species [69], providing a working example towards further future application of similar strategies to modulate *A. baumannii* overgrowth in poultry and other livestock.

2.3. Phage-antibiotic synergy

Phage-antibiotic synergy (PAS) refers to the usage of antibiotics at sublethal doses in combination to phage administration, with the aim of increasing the release of phage-progeny from bacterial cells [70]. PAS strategies might represent some advantages such as enhanced bacterial inhibition, reduced development of phage and penetration of biofilms [71]. However, care should be taken when considering a combined therapy, due to their unavoidable increased risk towards AMR insurgence. Low antibiotic doses used in such combinations could indeed facilitate the selection of resistant species, moreover the impact of these antibiotics on the rest of the microbiota symbionts, beyond the primary target, ought to be taken into consideration [72].

Importantly, the final PAS effect is affected by not only the qualitative distribution of antibiotics in the mix, but also by their relative concentrations. Ma Chao *et al.* optimised the multiplicity of infection (MOI, i.e., optimal phage/target ratio) of phages in combination with 8 different antibiotics applied to the control of *A. baumannii*, demonstrating that a reduction of rifampicin concentration led to a decreased PAS effect, otherwise increased by a decrease of both meropenem and minocycline concentrations [73]. On the other hand, the effectiveness of PAS, as a combined approach, has been shown in several studies. Indeed, Bartłomiej Grygorcewicz *et al.* observed approximately a 4-log reduction of *A. baumannii* when using vB_AbaP_AGC01 phage in combination to ciprofloxacin and meropenem, in a heat-inactivated plasma blood model [57]. Xin

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Tan *et al.* reported pathogen clearance and clinical improvement in patients previously diagnosed with carbapenem-resistant *A. baumannii* pneumonia, after treatment with monophage preparation in combination with tigecycline and polymyxin E [74].

2.4. Phage-encoded enzymes for the treatment of A. baumannii

2.4.1. Endolysins

Endolysins are phage-produced hydrolases that lyse bacterial cell walls allowing further release of progeny phages at the end of the replication cycle [75]. These enzymes are very effective towards peptidoglycan layers, leading to a sudden drop in osmotic pressure and therefore lysis [76]. According to their action on the main bonds in the peptidoglycan layer, endolysins divided into five categories: I) N-acetyl-β-D-intracellular amidase, II) N-acetyl-β-D-glucosaminidase, III) transglycosidase; IV) N-acetyl-leucoyl-l-alanine amidase and V) L-alaninoyl-D-glutamate endopeptidase [77]. The main advantage of endolysin therapy over traditional broad-spectrum antibiotics is their high specificity towards bacterial species or subspecies without interacting with the surrounding microbial cells [78]. Additionally, further endolysins advantages are connected to reduced resistance, to their synergistic activity with different antibacterial agents, and to their ability to play an effective role on biofilm and mucosal surface [79].

TS2631, an endolysin from the *Thermus scotoductus* bacteriophage vB_Tsc2631, can also lysate *A. baumannii* and *P. aeruginosa* [78]. Wu *et al*. overexpressed and purified endolysin (Ply6A3) from vB_AbaP_PD-6A3, demonstrating its ness towards 179 out of 552 clinical multidrug-resistant *A. baumannii* strains tested (32.4%). *In vitro*, Ply6A3 not only inhibited *A. baumannii* but also other strains such as *E. coli* and MSRA, indicating Ply6A3 activity targeting MSRA cell wall. During the observation period, no obvious side effects were observed after intraperitoneal injection of Ply6A3 in mice [79]. In another trial, the activity profiles of recombinant endotoxins firstly identified and isolated from members of the *Myoviridae* phage family（LysAm24, LysAp22, LysECD7, and LysSi3）[80], of were estimated towards one hundred Gram-negative pathogens, including clinical isolates, MDR *Klebsiella pneumoniae*, *Salmonella*, *P. aeruginosa*, *E. coli*, *A. baumannii*, and *Enterobacter spp*. Of the bacteria investigated, *A. baumannii* was the most sensitive to endolysin. The data showed that these enzymes did not promote the development of short-term drug resistance. Furthermore, LysSi3 and LysECD7. did not decrease *Bifidobacterium* and *Lactobacillus* abundance in humans [81]. In addition, LysAB54 from *A. baumannii* bacteriophage p54 showed high antibacterial activity against a variety of Gram-negative pathogens [82]. Free peptidoglycan within the gastrointestinal tract is another endolysin target. In monogastric farm animals, and poultry in particular, peptidoglycan in bacterial cell debris may detriment gastrointestinal functionality. Supplementation of microbial muramidase with endolysin activity has been shown to benefit growth performance and gastrointestinal functionality in broilers [83; 84; 85]. With poultry being a reservoir for MDRO, the use of endolysin based feed additives might assist to reduce the AMR level ending in the food chain.

2.4.2. Depolymerases

During biofilm formation, bacterial cells are usually surrounded by extracellular polymers (EPS), which can also act as barriers for phage penetration [88]. *A. baumannii* EPS increases the resistance of the bacterium to antimicrobial agents due to diffusion limitation and can lead to severe persistent infections that are particularly difficult to treat, also providing resistance to phages [89]. Depolymerases are phage-derived enzymes that facilitates the early stages of phage infection by degrading extracellular bacterial protein [90]. The depolymerase responsible for degrading EPS, or O-polysaccharides can be found

either as a virion component, or it can be secreted in a soluble form during bacterial cell lysis [91]. This unique ability of depolymerases to specifically recognize and degrade EPS and related biofilm components provides an attractive and promising tool for pathogen control [92]. On the other hand, biofilms are also known to develop within drinking lines in e.g. poultry production systems (Maes et al., 2019), pointing towards the use of depolymerases as a management practive implementation, also assisting AMR management. An example is provided by the tail spike protein derived from φAB6 with depolymerase activity, which can significantly inhibit the formation of and degrade existing biofilms, at concentration ≥0.78 ng [93]. Moreover, such proteins have also been found effective in reducing *A. baumannii* adhesion on the surface of medical devices [93].

2.5. Novel technologies applied to phage therapy

Recently, some technological developments based on phage therapy have been described, additionally to the traditional therapeutic schemes mentioned so far. One application is based on the work of Bei Ran *et al*. (2021), who developed a unique photodynamic antimicrobial agent (APNB) based on a cationic photosensitizer and a bacteriophage for precise bacterial eradication, also showing high efficacy against biofilm [94]. NB is a benzoxazine compound, which is a well-known DNA-binding dye with relatively low systemic toxicity, and in some cases also known for delaying tumoral growth. In this context, NB can direct selective phototoxicity in combination to phage therapy, increasing the effectiveness of the latter, which when used alone could not achieve optimal therapeutic result**s** [95]. The combination of the dye to the phage as an antimicrobial agent allows the real-time monitoring and evaluation of the treatment dynamics , based on the NB fluorescence. Further structural modification with e.g., sulphur atoms provide excellent reactive oxygen species generation ability, which could be used in combination with APNB specificity towards binding pathogenic microorganisms. Both *in vitro* and *in vivo* experiments demonstrated that APNB can effectively treat *A. baumannii* infection. Although, it ought to be mentioned that *A. baumannii* recovered faster after APNB treatment compared to ampicillin and polymyxin B in mice, APNB has promising application against MDRP and biofilm [51].

In terms of new technologies based on phage therapy, aerosol spray applied to both poultry and bedding material in production facilities may help prevent horizontal transmission of pathogens. Indeed, phage-based products can be used as biological disinfectants in hatcheries, farms, transport containers, poultry processing plants and food contact surfaces. Although not trialled against *A. baumannii*, bacteriophage-based surface disinfectants, such as BacWash TM (OmniLytics Inc., USA), targeting *Salmonella*, can be used as a cleaning agent. Similarly, Ecolicide PX™ (Intralytix) targeting *E. coli* O157:H7 has been developed to purify the skin of live animals prior to slaughter [96]. El-Gohary *et al*. [97] demonstrated that treating pads by spraying a bacteriophage preparation against *E. coli* could limit its spread in broilers. Similar phage therapy applications are rarely reported against *A. baumannii*, although based on these successful examples in poultry production, it is particularly important to study and include *A. baumannii* as a therapeutical target, both as a zoonotic agent and to limit the correlated spread of AMR.

3. Conclusions

Almost all the new recently developed antibiotics are variants of antibiotic classes discovered in the 1980s, however the currently reviewed and approved antibiotics inadequately address the challenges posed by the emergence and spread of AMR. Therefore, it is imperative to explore innovative approaches for the treatment of bacterial infections. Phage therapy represent an extremely promising, highly specific antimicrobial alternative. Phage mechanism of action relies on targeting and killing or inactivating sensitive bacteria specifically, and a variety of treatment options are under study at the moment

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as described in this review, with implications not only to humans, but also to poultry production. The latter is of rather importance, as reservoir for AMR and zoonotic bacteria. Efficacy and safety of phage therapy has been shown in the context of treatment of multidrug-resistant *A. baumannii*, through both *in vitro* and *in vivo* applications.

The current state of the art of the research on phage therapy is not comprehensive. Further clinical trials prior to successful routine applications in humans are rather important. In addition, several aspects of phage therapy require further elucidation, such as stability of the formulation, industrial scaling, coupled with intrinsic caveats related to the possible insurgence of bacteriophage resistance, phage coevolution with bacteria and broader effect on gut microbiota.

Conflicts of Interest:

The authors declare no conflict of interest

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References

[1] A. Howard, M. O'Donoghue, A. Feeney, and R.D. Sleator, Acinetobacter baumannii: an emerging opportunistic pathogen. Virulence 3 (2012) 243-50.

[2] P. Wang, R.Q. Li, L. Wang, W.T. Yang, Q.H. Zou, and D. Xiao, Proteomic Analyses of Acinetobacter baumannii Clinical Isolates to Identify Drug Resistant Mechanism. Frontiers in cellular and infection microbiology 11 (2021) 625430.

[3] C. Ayoub Moubareck, and D. Hammoudi Halat, Insights into Acinetobacter baumannii: A Review of Microbiological, Virulence, and Resistance Traits in a Threatening Nosocomial Pathogen. Antibiotics 9 (2020) 119.

[4] Environmental Phage-Based Cocktail and Antibiotic Combination Effects on Acinetobacter baumannii Biofilm in a Human Urine Model. Microbial Drug Resistance 27 (2021) 25-35.

[5] Antimicrobial resistance: 2014 global report on surveillance. (2014).

[6] K.M. Papp-Wallace, A. Endimiani, M.A. Taracila, and R.A. Bonomo, Carbapenems: Past, Present, and Future. Antimicrobial Agents and Chemotherapy 55 (2011) 4943-4960.

[7] C.R. Lee, J.H. Lee, M. Park, K.S. Park, I.K. Bae, Y.B. Kim, C.J. Cha, B.C. Jeong, and S.H. Lee, Biology of Acinetobacter baumannii: Pathogenesis, Antibiotic Resistance Mechanisms, and Prospective Treatment Options. Frontiers in cellular and infection microbiology 7 (2017) 55.

[8] S. Ibrahim, N. Al-Saryi, I.M.S. Al-Kadmy, and S.N. Aziz, Multidrug-resistant Acinetobacter baumannii as an emerging concern in hospitals.48 （2021）:6987-6998.

[9] M. Asif, I.A. Alvi, and S.U. Rehman, Insight into Acinetobacter baumannii: pathogenesis, global resistance, mechanisms of resistance, treatment options, and alternative modalities. Infection and drug resistance 11 (2018) 1249-1260.

[10] S.C. Nang, M.A.K. Azad, T. Velkov, Q.T. Zhou, and J. Li, Rescuing the Last-Line Polymyxins: Achievements and Challenges. Pharmacological reviews 73 (2021) 679-728.

[11] S. Girija As, and J.V. Priyadharsini, CLSI based antibiogram profile and the detection of MDR and XDR strains of Acinetobacter baumannii isolated from urine samples. Medical journal of the Islamic Republic of Iran 33 (2019) 3.

[12] S.F. Assimakopoulos, V. Karamouzos, A. Lefkaditi, C. Sklavou, F. Kolonitsiou, M. Christofidou, F. Fligou, C. Gogos, and M. Marangos, Triple combination therapy with high-dose ampicillin/sulbactam, high-dose tigecycline and colistin in the

treatment of ventilator-associated pneumonia caused by pan-drug resistant Acinetobacter baumannii: a case series study. Le infezioni in medicina 27 (2019) 11-16.

[13] Pan Drug-Resistant Environmental Isolate of Acinetobacter baumannii from Croatia. Microbial Drug Resistance 23 (2017) 494-496.

[14] A. Mottet, and G. Tempio, Global poultry production: current state and future outlook and challenges. World's Poultry Science Journal 73 (2017) 245-256.

[15] L. Chapot, L. Whatford, P. Compston, M. Tak, S. Cuevas, M. Garza, H. Bennani, H. Bin Aslam, M. Hennessey, G. Limon, K. Queenan, G. Fournié, N. Dadios, and B. Häsler, A Global Media Analysis of the Impact of the COVID-19 Pandemic on Chicken Meat Food Systems: Key Vulnerabilities and Opportunities for Building Resilience. Sustainability 13 (2021) 9435.

[16] S.J. More, European perspectives on efforts to reduce antimicrobial usage in food animal production. Irish veterinary journal 73 (2020) 2.

[17] F.P. Nocera, A.-R. Attili, and L. De Martino, Acinetobacter baumannii: Its Clinical Significance in Human and Veterinary Medicine. Pathogens 10 (2021) 127.

[18] S. Kumar, R. Anwer, M. Yadav, N. Sehrawat, V. Kumar, and A.K. Sharma, Isolation and Characterization of Acinetobacter baumannii from Chicken Meat Samples in North India. Asian Journal of Biological and Life sciences 10 (2021) 462-468.

[19] N. Release, WHO publishes list of bacteria for which new antibiotics are urgently needed. Neurosciences 38 (2017) 444-445.

[20] S. Sharma, S. Chatterjee, S. Datta, R. Prasad, D. Dubey, R.K. Prasad, and M.G. Vairale, Bacteriophages and its applications: an overview. Folia microbiologica 62 (2017) 17-55.

[21] S. Mäntynen, E. Laanto, H.M. Oksanen, M.M. Poranen, and S.L. Díaz-Muñoz, Black box of phage-bacterium interactions: exploring alternative phage infection strategies. Open biology 11 (2021) 210188.

[22] K.E. Kortright, B.K. Chan, J.L. Koff, and P.E. Turner, Phage Therapy: A Renewed Approach to Combat Antibiotic-Resistant Bacteria. Cell host & microbe 25 (2019) 219-232.

[23] R. Monteiro, D.P. Pires, A.R. Costa, and J. Azeredo, Phage Therapy: Going Temperate? Trends in microbiology 27 (2019) 368-378.

[24] D. Sun, K. Jeannot, Y. Xiao, and C.W. Knapp, Editorial: Horizontal Gene Transfer Mediated Bacterial Antibiotic Resistance. Frontiers in microbiology 10 (2019).

[25] N. Principi, E. Silvestri, and S. Esposito, Advantages and Limitations of Bacteriophages for the Treatment of Bacterial Infections. Frontiers in Pharmacology 10 (2019).

[26] M. Łobocka, K. Dąbrowska, and A. Górski, Engineered Bacteriophage Therapeutics: Rationale, Challenges and Future. BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy 35 (2021) 255-280.

[27] B. Isler, Y. Doi, R.A. Bonomo, and D.L. Paterson, New Treatment Options against Carbapenem-Resistant Acinetobacter baumannii Infections. Antimicrobial Agents and Chemotherapy 63 (2019) e01110-18.

[28] B. Isler, Y. Doi, R.A. Bonomo, and D.L. Paterson, New Treatment Options against Carbapenem-Resistant Acinetobacter baumannii Infections. Antimicrob Agents Chemother 63 (2019).

[29] B. Grygorcewicz, B. Wojciuk, M. Roszak, N. Łubowska, P. Błażejczak, J. Jursa-Kulesza, R. Rakoczy, H. Masiuk, and B. Dołęgowska, Environmental Phage-Based Cocktail and Antibiotic Combination Effects on Acinetobacter baumannii Biofilm in a Human Urine Model. Microbial drug resistance (Larchmont, N.Y.) 27 (2021) 25-35.

[30] S. LaVergne, T. Hamilton, B. Biswas, M. Kumaraswamy, R.T. Schooley, and D. Wooten, Phage Therapy for a Multidrug-Resistant Acinetobacter baumannii Craniectomy Site Infection. Open Forum Infectious Diseases 5 (2018) ofy064.

[31] F.M. Khan, V.S. Gondil, C. Li, M. Jiang, J. Li, J. Yu, H. Wei, and H. Yang, A Novel Acinetobacter baumannii Bacteriophage Endolysin LysAB54 With High Antibacterial Activity Against Multiple Gram-Negative Microbes. Frontiers in cellular and infection microbiology 11 (2021) 637313.

[32] L. Jiang, J. Tan, Y. Hao, Q. Wang, X. Yan, D. Wang, L. Tuo, Z. Wei, and G. Huang, Isolation and Characterization of a Novel Myophage Abp9 Against Pandrug Resistant Acinetobacater baumannii. Frontiers in microbiology 11 (2020) 506068.

[33] R.T. Schooley, B. Biswas, J.J. Gill, A. Hernandez-Morales, J. Lancaster, L. Lessor, J.J. Barr, S.L. Reed, F. Rohwer, S. Benler, A.M. Segall, R. Taplitz, D.M. Smith, K. Kerr, M. Kumaraswamy, V. Nizet, L. Lin, M.D. McCauley, S.A. Strathdee, C.A. Benson, R.K. Pope, B.M. Leroux, A.C. Picel, A.J. Mateczun, K.E. Cilwa, J.M. Regeimbal, L.A. Estrella, D.M. Wolfe, M.S. Henry, J. Quinones, S. Salka, K.A. Bishop-Lilly, R. Young, and T. Hamilton, Development and Use of Personalized Bacteriophage-Based Therapeutic Cocktails To Treat a Patient with a Disseminated Resistant Acinetobacter baumannii Infection. Antimicrobial Agents and Chemotherapy 61 (2017) e00954-17.

[34] C. Loc-Carrillo, and S.T. Abedon, Pros and cons of phage therapy. Bacteriophage 1 (2011) 111-114.

[35] S.S. Bochkareva, A.V. Aleshkin, O.N. Ershova, L.I. Novikova, and M.V. Zeigarnik, Anti-phage antibody response in phage therapy against healthcare-associated infections (HAIs). Infectious diseases 15(2017)35–40.

[36] S.L. Díaz-Muñoz, and B. Koskella, Bacteria-phage interactions in natural environments. Advances in applied microbiology 89 (2014) 135-83.

[37] M. Sari, R. Pilvi, and J. Matti, On-Demand Isolation of Bacteriophages Against Drug-Resistant Bacteria for Personalized Phage Therapy. Frontiers in microbiology 6 (2015) 1271-.

[38] S. Matsuzaki, M. Rashel, J. Uchiyama, S. Sakurai, T. Ujihara, M. Kuroda, M. Ikeuchi, T. Tani, M. Fujieda, H. Wakiguchi, and S. Imai, Bacteriophage therapy: a revitalized therapy against bacterial infectious diseases. Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy 11 (2005) 211-9.

[39] V. Krylov, O. Shaburova, S. Krylov, and E. Pleteneva, A genetic approach to the development of new therapeutic phages to fight pseudomonas aeruginosa in wound infections. Viruses 5 (2012) 15-53.

[40] R.J. Weld, C. Butts, and J.A. Heinemann, Models of phage growth and their applicability to phage therapy. Journal of theoretical biology 227 (2004) 1-11.

[41] R. Gupta, and Y. Prasad, Efficacy of polyvalent bacteriophage P-27/HP to control multidrug resistant Staphylococcus aureus associated with human infections. Current microbiology 62 (2011) 255-60.

[42] A. Górski, E. Jończyk-Matysiak, M. Łusiak-Szelachowska, R. Międzybrodzki, B. Weber-Dąbrowska, and J. Borysowski, The Potential of Phage Therapy in Sepsis. Frontiers in immunology 8 (2017) 1783.

[43] M. Skurnik, M. Pajunen, and S. Kiljunen, Biotechnological challenges of phage therapy. Biotechnol Lett 29(2007)995-1003

[44] S.M. Wienhold, J. Lienau, and M. Witzenrath, Towards Inhaled Phage Therapy in Western Europe. Viruses 11 (2019) pii: v11030295.

[45] M. Taati Moghadam, A. Khoshbayan, Z. Chegini, I. Farahani, and A. Shariati, Bacteriophages, a New Therapeutic Solution for Inhibiting Multidrug-Resistant Bacteria Causing Wound Infection: Lesson from Animal Models and Clinical Trials. Drug design, development and therapy 14 (2020) 1867-1883.

[46] B.K. Chan, S.T. Abedon, and C. Loc-Carrillo, Phage cocktails and the future of phage therapy. Future microbiology 8 (2013) 769-783.

[47] S. McCallin, S.A. Sarker, S. Sultana, F. Oechslin, and H. Brüssow, Metagenome analysis of Russian and Georgian Pyophage cocktails and a placebo-controlled safety trial of single phage versus phage cocktail in healthy Staphylococcus aureus carriers. Environmental microbiology 20 (2018) 3278-3293.

[48] F. Molina, A. Simancas, M. Ramírez, R. Tabla, I. Roa, and J.E. Rebollo, A New Pipeline for Designing Phage Cocktails Based on Phage-Bacteria Infection Networks. Frontiers in microbiology 12 (2021) 564532.

[49] T. Luong, A.C. Salabarria, and D.R. Roach, Phage Therapy in the Resistance Era: Where Do We Stand and Where Are We Going? Clinical therapeutics 42 (2020) 1659-1680.

[50] H. Oliveira, C. São-José, and J. Azeredo, Phage-Derived Peptidoglycan Degrading Enzymes: Challenges and Future Prospects for In Vivo Therapy. Viruses 10 (2018) pii: v10060292.

[51] B. Ran, Y. Yuan, W. Xia, M. Li, Q. Yao, Z. Wang, L. Wang, X. Li, Y. Xu, and X. Peng, A photo-sensitizable phage for multidrug-resistant Acinetobacter baumannii therapy and biofilm ablation. Chemical Science 12 (2021) 1054-1061.

[52] J. Jeon, J.-w. Kim, D. Yong, K. Lee, and Y. Chong, Complete Genome Sequence of the Podoviral Bacteriophage YMC/09/02/B1251 ABA BP, Which Causes the Lysis of an OXA-23-Producing Carbapenem-Resistant Acinetobacter baumannii Isolate from a Septic Patient. Journal of Virology 86 (2012) 12437-12438.

[53] Y. Hua, T. Luo, Y. Yang, D. Dong, R. Wang, Y. Wang, M. Xu, X. Guo, F. Hu, and P. He, Phage Therapy as a Promising New Treatment for Lung Infection Caused by Carbapenem-Resistant Acinetobacter baumannii in Mice. Frontiers in Microbiology 8 (2018)2659.

[54] M. Wu, K. Hu, Y. Xie, Y. Liu, D. Mu, H. Guo, Z. Zhang, Y. Zhang, D. Chang, and Y. Shi, A Novel Phage PD-6A3, and Its Endolysin Ply6A3, With Extended Lytic Activity Against Acinetobacter baumannii. Frontiers in microbiology 9 (2018) 3302.

[55] L. Jiang, J. Tan, Y. Hao, Q. Wang, X. Yan, D. Wang, L. Tuo, Z. Wei, and G. Huang, Isolation and Characterization of a Novel Myophage Abp9 Against Pandrug Resistant Acinetobacater baumannii. Frontiers in Microbiology 11 (2020) 625283.

[56] J.L. Wang, C.F. Kuo, C.M. Yeh, J.R. Chen, M.F. Cheng, and C.H. Hung, Efficacy of φkm18p phage therapy in a murine model of extensively drug-resistant Acinetobacter baumannii infection. Infection and drug resistance 11 (2018) 2301-2310.

[57] B. Grygorcewicz, M. Roszak, P. Golec, D. Śleboda-Taront, N. Łubowska, M. Górska, J. Jursa-Kulesza, R. Rakoczy, B. Wojciuk, and B. Dołęgowska, Antibiotics Act with vB_AbaP_AGC01 Phage against Acinetobacter baumannii in Human Heat-Inactivated Plasma Blood and Galleria mellonella Models. International Journal of Molecular Sciences 21 (2020) 4390.

[58] K.M. Styles, R. Thummeepak, U. Leungtongkam, S.E. Smith, G.S. Christie, A. Millard, J. Moat, C.G. Dowson, E.M.H. Wellington, S. Sitthisak, and A.P. Sagona, Investigating Bacteriophages Targeting the Opportunistic Pathogen Acinetobacter baumannii. Antibiotics 9 (2020) 200.

[59] M.M. Tawakol, N.M. Nabil, and A. Samy, Evaluation of bacteriophage efficacy in reducing the impact of single and mixed infections with Escherichia coli and infectious bronchitis in chickens. Infection ecology & epidemiology 9 (2019) 1686822.

[60] S. Hesse, and S. Adhya, Phage Therapy in the Twenty-First Century: Facing the Decline of the Antibiotic Era; Is It Finally Time for the Age of the Phage? Annual Review of Microbiology 73 (2019) 155-174.

[61] Y. Yuan, L. Wang, X. Li, D. Tan, C. Cong, and Y. Xu, Efficacy of a phage cocktail in controlling phage resistance development in multidrug resistant Acinetobacter baumannii. Virus research 272 (2019) 197734.

[62] N. Wu, J. Dai, M. Guo, J. Li, X. Zhou, F. Li, Y. Gao, H. Qu, H. Lu, J. Jin, T. Li, L. Shi, Q. Wu, R. Tan, M. Zhu, L. Yang, Y. Ling, S. Xing, J. Zhang, B. Yao, S. Le, J. Gu, J. Qin, J. Li, M. Cheng, D. Tan, L. Li, Y. Zhang, Z. Zhu, J. Cai, Z. Song, X. Guo, L.K. Chen, and T. Zhu, Pre-optimized phage therapy on secondary Acinetobacter baumannii infection in four critical COVID-19 patients. Emerging microbes & infections 10 (2021) 612-618.

[63] S.D. Upadhaya, J.M. Ahn, J.H. Cho, Y.K. Jin, and I. Kim, Bacteriophage cocktail supplementation improves growth performance, gut microbiome and production traits in broiler chickens. J Anim Sci Biotechnol 12 (2020)49.

[64] G.H. Shen, J.L. Wang, F.S. Wen, K.M. Chang, C.F. Kuo, C.H. Lin, H.R. Luo, and C.H. Hung, Isolation and characterization of phikm18p, a novel lytic phage with therapeutic potential against extensively drug resistant Acinetobacter baumannii. PLoS One 7 (2012) e46537.

[65] H.N. Jasim, R.R. Hafidh, and A.S. Abdulamir, Formation of therapeutic phage cocktail and endolysin to highly multi-drug resistant Acinetobacter baumannii: in vitro and in vivo study. Iranian journal of basic medical sciences 21 (2018) 1100-1108.

[66] B.K. Chan, S.T. Abedon, and C. Loc-Carrillo, Phage cocktails and the future of phage therapy. Future Microbiology 8 (2013) 769-783.

[67] A.S. Nilsson, Phage therapy—constraints and possibilities. Upsala Journal of Medical Sciences 119 (2014) 192–198.

 doi:10.20944/preprints202209.0037.v1

[68] M. Al Amin, M.N. Hoque, A.Z. Siddiki, S. Saha, and M.M. Kamal, Antimicrobial resistance situation in animal health of Bangladesh. Veterinary world 13 (2020) 2713-2727.

[69] P.J. Richards, P.L. Connerton, and I.F. Connerton, Phage Biocontrol of Campylobacter jejuni in Chickens Does Not Produce Collateral Effects on the Gut Microbiota. Frontiers in microbiology 10 (2019) 476.

[70] S. Xu, E. Campisi, J. Li, and V.A. Fischetti, Decontamination of Escherichia coli O157:H7 on fresh Romaine lettuce using a novel bacteriophage lysin. International journal of food microbiology 341 (2021) 109068.

[71] T.L. Tagliaferri, M. Jansen, and H.-P. Horz, Fighting Pathogenic Bacteria on Two Fronts: Phages and Antibiotics as Combined Strategy. Frontiers in Cellular and Infection Microbiology 9 (2019)22.

[72] F. Oechslin, Resistance Development to Bacteriophages Occurring during Bacteriophage Therapy. Viruses 10 (2018) 351.

[73] Chao Ma, Ning Wang, Yongping Xu, Bacteriophage combined with antibiotics in the control of multidrug-resistant Acinetobacter baumannii. Chinese Journal of Antibiotics 43 (2018) 9.

[74] X. Tan, H. Chen, M. Zhang, Y. Zhao, Y. Jiang, X. Liu, W. Huang, and Y. Ma, Clinical Experience of Personalized Phage Therapy Against Carbapenem-Resistant Acinetobacter baumannii Lung Infection in a Patient With Chronic Obstructive Pulmonary Disease. Frontiers in cellular and infection microbiology 11 (2021) 631585.

[75] R. Young, Bacteriophage lysis: mechanism and regulation. Microbiological reviews 56 (1992) 430-81.

[76] M. Schmelcher, and M.J. Loessner, Bacteriophage endolysins - extending their application to tissues and the bloodstream. Current opinion in biotechnology 68 (2021) 51-59.

[77] L. Blasco, A. Ambroa, R. Trastoy, I. Bleriot, M. Moscoso, L. Fernández-Garcia, E. Perez-Nadales, F. Fernández-Cuenca, J. Torre-Cisneros, J. Oteo-Iglesias, A. Oliver, R. Canton, T. Kidd, F. Navarro, E. Miró, A. Pascual, G. Bou, L. Martínez-Martínez, and M. Tomas, In vitro and in vivo efficacy of combinations of colistin and different endolysins against clinical strains of multi-drug resistant pathogens Sci Rep 10(2020)7163.

[78] M. Plotka, M. Kapusta, S. Dorawa, A.-K. Kaczorowska, and T. Kaczorowski, Ts2631 Endolysin from the Extremophilic Thermus scotoductus Bacteriophage vB_Tsc2631 as an Antimicrobial Agent against Gram-Negative Multidrug-Resistant Bacteria. Viruses 11 (2019) 657.

[79] M. Wu, K. Hu, Y. Xie, Y. Liu, D. Mu, H. Guo, Z. Zhang, Y. Zhang, D. Chang, and Y. Shi, A Novel Phage PD-6A3, and Its Endolysin Ply6A3, With Extended Lytic Activity Against Acinetobacter baumannii. Frontiers in Microbiology 9 (2019)3302.

[80] N.P. Antonova, D.V. Vasina, A.M. Lendel, E.V. Usachev, V.V. Makarov, A.L. Gintsburg, A.P. Tkachuk, and V.A. Gushchin, Broad Bactericidal Activity of the Myoviridae Bacteriophage Lysins LysAm24, LysECD7, and LysSi3 against Gram-Negative ESKAPE Pathogens. Viruses 11 (2019) pii: v11030284.

[81] D.V. Vasina, N.P. Antonova, I.V. Grigoriev, V.S. Yakimakha, A.M. Lendel, M.A. Nikiforova, A.A. Pochtovyi, T.A. Remizov, E.V. Usachev, N.V. Shevlyagina, V.G. Zhukhovitsky, M.V. Fursov, V.D. Potapov, A.M. Vorobev, A.V. Aleshkin, A.I. Laishevtsev, V.V. Makarov, S.M. Yudin, A.P. Tkachuk, and V.A. Gushchin, Discovering the Potentials of Four Phage Endolysins to Combat Gram-Negative Infections. Frontiers in Microbiology 12 (2021) 748718.

[82] F.M. Khan, V.S. Gondil, C. Li, M. Jiang, J. Li, J. Yu, H. Wei, and H. Yang, A Novel Acinetobacter baumannii Bacteriophage Endolysin LysAB54 With High Antibacterial Activity Against Multiple Gram-Negative Microbes. Frontiers in Cellular and Infection Microbiology 11 (2021) 637313.

[83] J. Lichtenberg, E. Perez Calvo, K. Madsen, T. Østergaard Lund, F. Kramer Birkved, S. van Cauwenberghe, M. Mourier, L. Wulf-Andersen, A.J.M. Jansman, and R. Lopez-Ulibarri, Safety evaluation of a novel muramidase for feed application. Regulatory toxicology and pharmacology : RTP 89 (2017) 57-69.

[84] F. Goodarzi Boroojeni, K. Männer, J. Rieger, E. Pérez Calvo, and J. Zentek, Evaluation of a microbial muramidase supplementation on growth performance, apparent ileal digestibility, and intestinal histology of broiler chickens. Poultry science 98 (2019) 2080-2086.

[85] M. Sais, A.C. Barroeta, P. López-Colom, M. Nofrarías, N. Majó, R. Lopez-Ulibarri, E. Pérez Calvo, and S.M. Martín-Orúe, Evaluation of dietary supplementation of a novel microbial muramidase on gastrointestinal functionality and growth performance in broiler chickens. Poultry science (2019) pii: 5545669.

[86] F. Abdelrahman, M. Easwaran, O.I. Daramola, S. Ragab, S. Lynch, T.J. Oduselu, F.M. Khan, A. Ayobami, F. Adnan, E. Torrents, S. Sanmukh, and A. El-Shibiny, Phage-Encoded Endolysins. Antibiotics 10 (2021) 124.

[87] M.u. Rahman, W. Wang, Q. Sun, J.A. Shah, C. Li, Y. Sun, Y. Li, B. Zhang, W. Chen, and S. Wang, Endolysin, a Promising Solution against Antimicrobial Resistance. Antibiotics 10 (2021) 1277.

[88] H.C. Flemming, J. Wingender, U. Szewzyk, P. Steinberg, S.A. Rice, and S. Kjelleberg, Biofilms: an emergent form of bacterial life. Nature reviews. Microbiology 14 (2016) 563-75.

[89] G.P.C. Salmond, and P.C. Fineran, A century of the phage: past, present and future.. Nat Rev Microbiol 13(2015):777-786

[90] D.P. Pires, H. Oliveira, L.D. Melo, S. Sillankorva, and J. Azeredo, Bacteriophage-encoded depolymerases: their diversity and biotechnological applications. Applied microbiology and biotechnology 100 (2016) 2141-51.

[91] A. Latka, B. Maciejewska, G. Majkowska-Skrobek, Y. Briers, and Z. Drulis-Kawa, Bacteriophage-encoded virion-associated enzymes to overcome the carbohydrate barriers during the infection process. Applied microbiology and biotechnology 101 (2017) 3103-3119.

[92] C. Wang, P. Li, Y. Zhu, Y. Huang, M. Gao, X. Yuan, W. Niu, H. Liu, H. Fan, Y. Qin, Y. Tong, Z. Mi, and C. Bai, Identification of a Novel Acinetobacter baumannii Phage-Derived Depolymerase and Its Therapeutic Application in Mice. Frontiers in Microbiology 11 (2020)1407.

[93] M. Shahed-Al-Mahmud, R. Roy, F.G. Sugiokto, M.N. Islam, M.-D. Lin, L.-C. Lin, and N.-T. Lin, Phage φAB6-Borne Depolymerase Combats Acinetobacter baumannii Biofilm Formation and Infection. Antibiotics 10 (2021) 279.

[94] S. Maes, T. Vackier, S. Nguyen Huu, M. Heyndrickx, H. Steenackers, I. Sampers, K. Raes, A. Verplaetse, and K. De Reu, Occurrence and characterisation of biofilms in drinking water systems of broiler houses. BMC microbiology 19 (2019) 77.

[95] K. Hirakawa, K. Ota, J. Hirayama, S. Oikawa, and S. Kawanishi, Nile blue can photosensitize DNA damage through electron transfer. Chemical research in toxicology 27 (2014) 649-55.

[96] J. Sommer, C. Trautner, A.K. Witte, S. Fister, D. Schoder, P. Rossmanith, and P.J. Mester, Don't Shut the Stable Door after the Phage Has Bolted-The Importance of Bacteriophage Inactivation in Food Environments. Viruses 11 (2019). pii: v11050468

[97] F.A. El-Gohary, W.E. Huff, G.R. Huff, N.C. Rath, Z.Y. Zhou, and A.M. Donoghue, Environmental augmentation with bacteriophage prevents colibacillosis in broiler chickens. Poultry Science 93 (2014) 2788-92.