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Editorial

Rediscovering Phage Therapy: Promising Approach for Combating Antimicrobial Resistance

Obujanje fagne terapije: obetaven pristop za boj s protimikrobno odpornostjo

Key words

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Antimicrobial resistance (AMR) is a concerning public health threat which affects human and animal health as well as the environment. The rapid spread of bacterial strains resistant to clinically used antibacterials necessitates the exploration and utilization of different treatment options. Phage therapy, the use of bacterial viruses – bacteriophages – to treat bacterial infections, has gained renewed interest as an aid in addressing AMR. As we outline in this editorial, the introduction and widespread use of phage therapy in human and veterinary medicine faces regulatory challenges. However, the recent adoption of new guidelines and other regulatory developments in this area will facilitate the progress of phage therapy.

Antimicrobial resistance was responsible for 1.2 million deaths globally in 2019 (1). The most pessimistic projections estimate 10 million deaths per year in 2050, meaning AMR will be more deadly than cancer, if no action is taken (2,3). Bacteria carrying antibiotic resistance genes can be transmitted between humans, animals, plants and the environment. Therefore, the fight against AMR requires unified and multidisciplinary action (OneHealth approach). Although livestock farming accounts for up to 80 % of total antibiotic consumption, infections in companion animals are predominantly treated with human antibiotics. As a result, pets become reservoirs for zoonotic bacterial species carrying resistance

Protimikrobna odpornost (AMR) predstavlja resno grožnjo javnemu zdravju in vpliva tako na zdravje ljudi in živali kot na okolje. Hitro širjenje bakterijskih sevov, ki so odporni na klinično uporabljane protibakterijske učinkovine, zahteva raziskovanje in uporabo drugačnih možnosti zdravljenja. Fagna terapija, uporaba bakterijskih virusov – bakteriofagov – za zdravljenje bakterijskih okužb, je pridobila ponovno zanimanje kot pomoč pri reševanju problema protimikrobne odpornosti. Kot opisujemo v tem uvodniku, se uvedba in široka uporaba fagne terapije v humani in veterinarski medicini sooča z regulatornimi izzivi, vendar pa bo nedavno sprejetje novih smernic in razvoj drugih regulatornih predpisov na tem področju olajšal napredek zdravljenja s fagi.

Protimikrobna odpornost je leta 2019 povzročila 1,2 milijona smrti po celem svetu (1). Najbolj pesimistične napovedi ocenjujejo, da bi lahko, če ne bomo ukrepali, leta 2050 zaradi protimikrobne odpornosti umrlo 10 milijonov ljudi na leto, kar pomeni, da bo povzročila več smrti kot rak (2,3). Bakterije, ki nosijo gene za odpornost na protibakterijske učinkovine, se lahko prenašajo med ljudmi, živalmi, rastlinami in okoljem, zato boj proti protimikrobni odpornosti zahteva enotno in multidisciplinarno delovanje (pristop OneHealth). Čeprav se v živinoreji porabi do 80 % celotne porabe protibakterijskih učinkovin, se okužbe domačih živali večinoma zdravijo

genes of clinical importance to humans (4–6). As outlined in the review article, published in this issue, canine skin infections are a frequent complication in small animal medicine, where the prevalence of antimicrobialresistant bacteria is increasing, necessitating additional treatment approaches such as vaccines and phage therapy (7).

Phage therapy is a treatment option based on natural predators of bacteria, the bacteriophages (phages). Their antibacterial mechanism of action differs from that of antibiotics and enables an effect on antimicrobial-resistant bacteria without causing cross-resistance. In addition, phages have a narrow host range, which prevents undesirable effects on the microbiota. They are non-toxic, can of self-replicate at the site of infection and have anti-biofilm activity (8,9). Their therapeutic potential was recognized as early as 1919, when Felix d'Herelle used phages to treat dysentery (10). The clinical success of these initial trials encouraged further applications, from the treatment of staphylococcal skin diseases to cholera and bubonic plague (10). Despite the promising initial results, early controversies in phage clinical research, inadequate understanding of phage biology and political reasons topped with the discovery of antibiotics pushed phage therapy into obscurity in Western countries (11). With the rise of AMR, phages are regaining the importance and attention of scientific and business community investing considerable efforts into development of novel phage-based antibacterial therapeutics. The poorly defined regulatory status of phages has been a bottleneck. However, the European Medicines Agency (EMA) has recently published Guideline on quality, safety and efficacy of veterinary medicinal products specifically designed for phage therapy, providing a regulatory framework for the use of phage therapy products in veterinary medicine. Phage therapies are classified as novel therapies by Regulation (EU) 2019/6 and require a centralized marketing authorization procedure involving clinical trials (12). Although the guidelines offer some flexibility, e.g. multiphage compositions can be regularly updated or reconditioned due to the narrow host range and development of resistance, the path to product authorization is expected to be long and expensive. Marketing authorization is not required for prescription medicinal products prepared in a pharmacy, so called magistral formulae, which are manufactured according to European Pharmacopoeia (Ph. Eur.). In July 2024, the European Pharmacopoeia Commission (EPC) will adopt a new general chapter in the European Pharmacopoeia, which will cover phage therapy medicinal products. The chapter provides requirements for the production and quality control of phage therapy products for human and veterinary use and is already pre-published on the European Directorate for the Quality of Medicines & HealthCare (EDQM) website (13). This document will facilitate the use of phage magistral preparations throughout the EU allowing more personalized approach, as was already in practice in Belgium for human use (14). The regulatory guidelines make it clear, that not all phages are suitable for phage therapy. The most important phage characteristic for therapy is their lytic lifestyle, which ensures the killing of bacteria at the end of their replication cycle. In addition, therapeutic

z učinkovinami razvitimi za humano uporabo. Posledično postajajo hišni ljubljenčki rezervoarji za zoonotske bakterijske vrste, ki prenašajo gene za odpornost, ki so klinično pomembni za ljudi (4–6). Kot je poudarjeno v preglednem članku, objavljenem v tej izdaji, so pasje okužbe kože pogost zaplet v medicini malih živali, kjer narašča razširjenost odpornih bakterij, zaradi česar so za zdravljenje potrebni dodatni pristopi, kot so cepiva in fagna terapija (7).

Fagna terapija je možnost zdravljenja, ki temelji na naravnih zajedavcih bakterij, bakteriofagih (fagih). Njihov protibakterijski mehanizem delovanja se razlikuje od mehanizma delovanja protibakterijskih učinkovin in omogoča delovanje na odporne bakterije brez povzročitve navzkrižne odpornosti. Poleg tega imajo fagi ozek nabor gostiteljev, kar preprečuje neželene učinke na mikrobioto, niso toksični, lahko se samo-podvojujejo na mestu okužbe in delujejo proti bakterijskim biofilmom (8,9). Njihov terapevtski potencial je bil prepoznan že leta 1919, ko je Felix d'Herelle uporabil fage za zdravljenje dizenterije (10). Klinični uspeh začetnih preskušanj je spodbudil nadaljnjo uporabo, od zdravljenja stafilokoknih kožnih bolezni do kolere in bubonske kuge (10). Kljub obetavnim začetnim rezultatom so zgodnje polemike v kliničnih raziskavah fagov, neustrezno razumevanje biologije fagov, politični razlogi, poleg ega pa še odkritje protibakterijskih učinkovin, potisnili fagno terapijo v zahodnih državah v pozabo (11). Z vzponom protimikrobne odpornosti fagi ponovno pridobivajo pomembnost in pozornost znanstvene skupnosti in industrije, ki vlaga veliko truda v razvoj novih protibakterijskih terapij na osnovi fagov. Težavo je dolgo predstavljal slabo definiran egulatorni status fagov, vendar pa je Evropska agencija za zdravila (EMA) nedavno objavila Smernice o kakovosti, varnosti in učinkovitosti zdravil za uporabo v veterinarski medicini, posebej zasnovanih za terapijo s fagi, ki zagotavljajo regulatorni okvir za uporabo izdelkov za agno terapijo v veterinarski medicini. Fagne terapije so z Uredbo (EU) 2019/6 razvrščene kot nove terapije in zahtevajo centraliziran postopek pridobitve dovoljenja za promet, ki vključuje klinična preskušanja (12). Čeprav smernice omogočajo nekaj prilagodljivosti, npr. fagne koktejle je mogoče redno posodabljati ali obnavljati zaradi ozkega obsega gostiteljev in razvoja odpornosti, se pričakuje, da bo pot do odobritve izdelka dolga in draga. Za zdravila na recept, tako imenovana magistralna zdravila, ki so pripravljena v lekarni, in so izdelana v skladu z Evropsko farmakopejo (Ph. Eur.), registracija ni potrebna. Julija 2024 bo Komisija za Ph. Eur. sprejela novo splošno poglavje Evropske farmakopeje, ki bo zajemalo zdravila za fagno terapijo. Poglavje določa zahteve za proizvodnjo in nadzor kakovosti fagnih terapevtskih izdelkov za humano in veterinarsko uporabo, osnutek je na voljo v predogled na spletni strani Evropskega direktorata za kakovost zdravil (EDQM) (13). Ta dokument bo olajšal uporabo fagnih magistralnih pripravkov po vsej EU, kar bo omogočilo personaliziran pristop, kot je za humano uporabo že v praksi v Belgiji (14). Regulatorne smernice jasno navajajo, da vsi fagi niso primerni za terapijo. Najpomembnejša značilnost terapevtskih fagov je njihov litični življenjski slog, ki zagotavlja uničenje bakterij na koncu

phages should not contain genetic elements encoding toxins, virulence factors, antibiotic resistance and lysogeny-related genes (15).

Several classes of phage-based products are currently under development, either for use in humans, veterinary medicine or the environment. Phages isolated from environmental sources, are referred to as natural phages. Although they may be suitable for therapeutic applications, they cannot be readily patented, which makes them less attractive for drug development. Nevertheless, natural phages are convenient for use in magistral preparations and there are several research groups, collecting natural phages in biobanks available for the most critical clinical cases (16). Genetically engineered phages are modified to increase their efficacy (improving host range or delaying the emergence of phage-resistant bacteria), or to improve their pharmacokinetics (17). Although the extent of the clinical superiority of genetically engineered phages is currently unclear, patentability of these phages attracts investors and enables the development of such products. Another class of phage-based products are phage proteins with antibacterial activity, such as endolysins and depolymerases, as reviewed in (18). As these are proteins by nature, they are subject to different regulatory requirements and there are fewer intellectual property protection issues than with natural phages.

Phage therapy and phage-based products are an important additional treatment option for bacterial infections, which will never completely replace antibiotics. However, with increasing AMR and associated problems, it is crucial to invest in phage research and development to expand the toolbox of weapons against deadly bacterial infections.

njihovega replikacijskega cikla. Poleg tega terapevtski fagi ne smejo vsebovati genetskih elementov, ki kodirajo toksine, virulentne dejavnike, odpornost na antibiotike in genov povezanih z lizogenim ciklom (15).

Trenutno je v razvoju več razredov izdelkov na osnovi fagov, bodisi za uporabo pri ljudeh, v veterinarski medicini bodisi okolju. Fage, izolirane iz okolja, imenujemo naravni fagi. Čeprav so lahko primerni za terapevtske aplikacije, jih ni mogoče enostavno patentirati, zaradi česar so manj privlačni za razvoj zdravil. Kljub temu so primerni za uporabo v magistralnih pripravkih in obstaja več raziskovalnih skupin po svetu, ki naravne fage zbirajo v biobanke s čimer omogočajo fage za zdravljenje najbolj kritičnih kliničnih primerov (16). Gensko spremenjeni fagi so spremenjeni z namenom povečanja njihove učinkovitosti (razširitev obsega gostiteljev ali odložitev pojava na fage odpornih bakterij) ali za izboljšanje njihove farmakokinetike (17). Čeprav obseg klinične superiornosti gensko spremenjenih fagov trenutno še ni jasen, možnost patentne zaščite takih produktov privablja vlagatelje in omogoča sredstva za razvoj takšnih izdelkov. Drug razred izdelkov na osnovi fagov so fagni proteini s protibakterijskim delovanjem, kot so endolizini in depolimeraze, kot je opisano v (18). Ker so to po naravi beljakovine, zanje veljajo drugačne regulatorne zahteve, poleg tega je v teh primerih manj težav z zaščito intelektualne lastnine kot pri naravnih fagih.

Fagna terapija in izdelki na osnovi fagov so pomembna dodatna možnost zdravljenja bakterijskih okužb, ki ne bodo nikoli popolnoma nadomestili protibakterijskih učinkovin. Vendar pa je zaradi naraščajoče protimikrobne odpornosti in s tem povezanih težav ključno vlagati v raziskave in razvoj fagov, da bi razširili nabor orožja proti smrtonosnim bakterijskim okužbam.

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