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Review

Bacteriophages in the control of pathogenic vibrios

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ABSTRACT

Vibrios are common inhabitants of marine and estuarine environments. Some of them can be pathogenic to humans and/or marine animals using a broad repertory of virulence factors. Lately, several reports have indicated that the incidence of *Vibrio* infections in humans is rising and also in animals constitute a continuing threat for aquaculture. Moreover, the continuous use of antibiotics has been accompanied by an emergence of antibiotic resistance in *Vibrio* species, implying a necessity for efficient treatments. One promising alternative that emerges is the use of lytic bacteriophages; however, there are some drawbacks that should be overcome to make phage therapy a widely accepted method. In this work, we discuss about the major pathogenic *Vibrio* species and the progress, benefits and disadvantages that have been detected during the experimental use of bacteriophages to their control.

Contents

1. Introduction

Vibrios are Gram-negative bacteria that can be found in marine and estuarine environments. This genus comprises several pathogenic species for humans and animals. The most clinically important pathogens for humans are *Vibrio cholerae* [1], *V. parahaemolyticus* [2] and *V. vulnificus* [3]; however, other species such as *V. fluvialis* and *V. mimicus* have been also associated with clinical cases [4,5]. *V. cholerae*

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is responsible for several large outbreaks of cholera, including Haiti in 2011 [6], while *V. parahaemolyticus*, although is able to cause severe mortality in aquatic animal species [7,8], in this case will be considered as human pathogen since is a major cause of severe diarrhea and human acute gastroenteritis worldwide [2]. *V. parahaemolyticus* is also the most common non-cholera *Vibrio* species reported to cause infection. However, the most lethal food-transmitted pathogen in USA and possibly in the world is *V. vulnificus* [3].

On the other hand, the major pathogenic vibrios for animals are *V. anguillarum*, *V. ordalii* and *Vibrio harveyi*. The first two are the ones responsible of classic vibriosis that can affect more than 50 species of marine animals [9,10], while the latter is a recurrent pathogen for aquaculture industry associated with warm waters [11]. There are also other controversial species such as *V. alginolyticus* because strains of this species, in addition to being reported as human emerging pathogen [12,13], and pathogenic for marine animals [14,15], while other have been suggested for potential use as probiotics in aquaculture [16,17]. In this case this species will be considered as marine animal pathogen.

Similarly to other animal production industries, antibiotics are used in aquaculture to control bacterial diseases, and even with prophylactic purposes. However, the use and abuse of antibiotics have led to the proliferation of multiples pathogens resistant to antibiotics. In 2014, the World Health Organization (WHO) has raised the alert against the antibiotic resistance [18], and vibrios are not the exception for this problem. Antibiotic resistance has been reported in several strains of this genus, from clinical and environmental origin [19,20,21,22]. The lack of effective treatments to control pathogenic vibrios resistant to antibiotics has led to the exploration of new alternatives. One of the most promising options is the use of lytic bacteriophages to kill pathogenic bacteria [23]. Bacteriophages are the most abundant biological entity on Earth [24,25], and they play a fundamental role in the evolution of bacteria [26,27]. Unlike antibiotics, bacteriophages are specific; therefore, their application will not disturb non-target bacterial species. Besides, they are not toxic and self-restricted, then, will remain in the environment only if the host bacteria are present [28].

This review summarizes the principal aspects of *Vibrio* as pathogens for humans and animals, as well as the principal advances, benefits and disadvantages in the use of bacteriophages to control these pathogenic bacteria. We discuss the main challenges that must be overcome in order to extend its applicability and to advance from an experimental alternative to a first choice treatment.

2. Principal pathogenic vibrios

2.1. Pathogenic vibrios in humans

There are at least twelve species of *Vibrio* which are known to be human pathogens. These species include *V. alginolyticus*, *V. cholerae*, *V. cincinnatiensis*, *V. damsela*, *V. fluvialis*, *V. furnisii*, *V. metschnikovii*, *V. mimicus*, *V. parahaemolyticus* and *V. vulnificus* among others [1,2,3,5, 29,30]. They can cause three major syndromes of clinical illness, such as gastroenteritis, wound infections and septicemia, being the most common clinical manifestation a self-limiting gastroenteritis. *V. cholerae*, *V. parahaemolyticus*, *V. vulnificus* in a greater extent, and *V. alginolyticus, V. fluvialis* and *V. mimicus* in a lesser extent, are the most important in the clinical microbiology and food safety fields. These pathogens have diverse virulence factors to elicit illness in human, being *V. vulnificus* and *V. alginolyticus* primarily associated with extraintestinal infections [3,12] while *V. parahaemolyticus, V. mimicus* and *V. cholerae* are mainly related to gastroenteritis cases (Fig. 1) [2, 31,32].

Unlike other *Vibrio spp.* which occur naturally in seafood, *V. cholerae* is primarily found in water or food sources contaminated with feces although it can also be found in the brackish river and coastal waters. At date, *V. cholerae* has been the most studied *Vibrio* due to its impact on public health and the severity of the cholera disease [1,31]. Among several virulence factors produced by this pathogen, the main ones are the cholera toxin (CT) [33], which is provided by a bacteriophage [34], the toxin co-regulated pilus (TCP) and others that facilitate its colonization in the intestine, all of them under the control of the ToxR regulon (Fig. 1) [35,36]. During infection, *V. cholerae* causes watery diarrhea, often fatal if untreated, and it is responsible for approximately between 3–5 million cases and over 100,000 deaths each year around the world according to the Center for Disease Control and Prevention (CDC) in 2017 [37].

The most common non-cholera *Vibrio* infection reported is *V. parahaemolyticus* [2,38]. Human infections caused by these bacteria are mainly produced after the consumption of raw or undercooked shellfish; only in the Unites States, this pathogen causes 45,000 illnesses each year. In fact, since 1996, the appearances of the

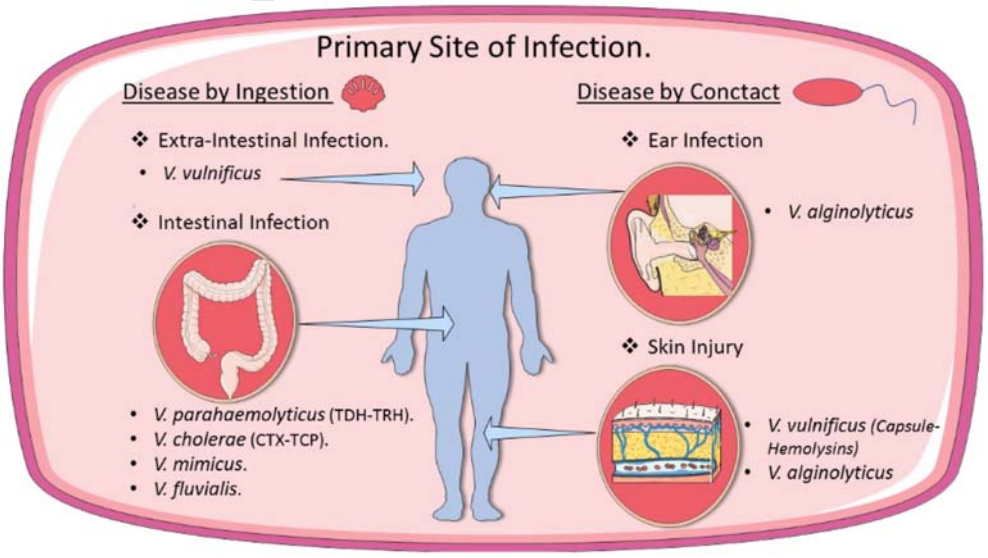

Fig. 1. Primary site of infection of different pathogenic Vibrio affecting humans. There are several species of pathogenic vibrios infecting humans. Some of them such as *V. cholerae* or *V. parahaemolyticus* are well characterized and their principal virulence factors have been identified while other species such as *V. mimicus* or *V. alginolyticus* are considered emergent pathogens. Infections produced by vibrios can be acquired by ingestion of contaminated food or direct contact with the bacteria, colonizing different sites in human body.

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