



## REVIEW IN GASTROENTEROLOGY

### Role of *Helicobacter pylori* coccoid forms in infection and recrudescence<sup>☆</sup>



Muhannad Sarem<sup>a,\*</sup>, Rodolfo Corti<sup>b</sup>

<sup>a</sup> Instituto Universitario de Ciencias de la Salud, Facultad de Medicina, Fundación H. A. Barceló, Ciudad Autónoma de Buenos Aires, Argentina

<sup>b</sup> Unidad de Esófago y Estómago, Hospital Bonorino Udaondo, Ciudad Autónoma de Buenos Aires, Argentina

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**Abstract** *Helicobacter pylori* is a spiral Gram-negative bacillus, which colonizes the human stomach and plays a key role in the pathogenesis of a number of gastroduodenal diseases. However, when exposed to environmental stressed conditions, such as increased oxygen tension, extended incubation and exposure to antibiotics, *H. pylori* is able to enter the viable but nonculturable state, in which the bacterium modifies its morphology from a spiral to coccoid form, as a manifestation of cell adaptation to these adverse conditions. In gastric tissues, viable coccoid forms may remain latent for long time and retain virulence factors, so these forms possibly contribute to the treatment failures and recurrence of *H. pylori* infection and gastroduodenal diseases as well. In this review, we will discuss several aspects of cellular adaptation and survival of *H. pylori*, antibiotic susceptibility and virulence of coccoid forms and its involvement with recrudescence.

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#### PALABRAS CLAVE

Formas cocoides de *Helicobacter pylori*;  
Virulencia de las formas cocoides;  
Recrudescencia

#### Rol de las formas cocoides de *Helicobacter pylori* en la infección y la recrudescencia

**Resumen** *Helicobacter pylori* es un bacilo espiral gramnegativo que coloniza el estómago humano y desempeña un papel clave en la patogénesis de diferentes enfermedades gastroduodenales. Sin embargo, cuando se expone a condiciones de estrés ambientales, tales como el aumento de la tensión de oxígeno, la incubación prolongada o la exposición a antibióticos, *Helicobacter pylori* entra en un estado viable pero no cultivable, en el cual la bacteria

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\* Corresponding author.

E-mail address: [msarem@hotmail.com](mailto:msarem@hotmail.com) (M. Sarem).

modifica su morfología de una forma bacilar a una cocoide como manifestación de adaptación celular a estas condiciones adversas. En el tejido gástrico, las formas cocoides viables pueden permanecer latentes durante mucho tiempo y retener factores de virulencia, por lo que estas formas posiblemente puedan contribuir a los fracasos del tratamiento y la recurrencia de la infección y de las enfermedades gastroduodenales también. En esta revisión se discutirán varios aspectos de la adaptación celular y supervivencia de *Helicobacter pylori*, la susceptibilidad a los antibióticos y la virulencia de las formas cocoides y su participación en la recrudescencia. © 2015 Elsevier España, S.L.U. and AEEH y AEG. Todos los derechos reservados.

## Introduction

*Helicobacter pylori* (*H. pylori*) is a Gram-negative microaerophilic bacterium, whose natural habitat is the stomach. Although it typically has a bacillary form with several flagella at one end, it adopts a coccoid appearance in unfavourable environmental conditions.<sup>1,2</sup>

*H. pylori* is a major aetiological factor in active chronic gastritis, peptic ulcer, gastric mucosa-associated lymphoid tissue (MALT) lymphoma and gastric cancer. Although the bacterium is estimated to be present in the gastric mucosa of half the world's population, these diseases only develop in approximately 15–20% of colonized individuals.<sup>2,3</sup>

The most common treatment regimens have resulted in an eradication rate of around 85% in many geographical areas,<sup>4–6</sup> but efficacy has been compromised, especially in recent years, by the rapid emergence of antibiotic-resistant strains and poor treatment adherence.<sup>5,7</sup>

It is important to consider that the cure (as well as prevention of complications) for active chronic gastritis and peptic ulcer and for some low-grade forms of gastric MALT lymphoma depends on the success of *H. pylori* eradication. Furthermore, ensuring and sustaining successful eradication of this microorganism in all its biological forms would prevent recrudescence of the infection and, therefore, disease relapses.

The aim of this review is to present a general overview of the coccoid form of *H. pylori*, highlighting its microbiological profile, antibiotic susceptibility and virulence. Its involvement in gastric disease will also be analyzed, and the extent to which it is associated with infection recrudescence and disease relapse will be examined.

## Survival and cellular adaptation of *H. pylori*

### General considerations

All living organisms are equipped with mechanisms that enable them to survive in adverse environments. For some, their response implies (in addition to metabolic adaptations) changes to cell morphology.<sup>8,9</sup> Several microorganisms have the ability to differentiate into a viable but non-culturable (VBNC) state in response to environmental conditions that are unfavourable to survival and growth. This strategy is

widely used by microorganisms such as *Salmonella*, *Campylobacter* and *Escherichia*.<sup>10,11</sup>

In the VBNC state, bacteria generally decrease their size and change shape to become small spherical bodies. They reduce their respiration rate and nutrient transport and change gene expression and molecular synthesis. In this state they cannot be detected using conventional culture techniques. However, changes in environmental conditions may lead these microorganisms to either “revive” (and reconvert to their active state) or degenerate.<sup>10–13</sup>

Similarly, *H. pylori*, when it experiences harmful environmental conditions (in or outside its natural habitat), changes its classic bacillary form and enters a VBNC state that leads to morphological and metabolic changes as well as modifications in growth behaviour.<sup>14,15</sup>

### Viable but non-culturable state of *H. pylori*

Although some authors initially tried to demonstrate that the conversion from bacillary to coccoid form was a passive process that resulted in cell death and, therefore, that the coccoid forms were the degenerated remains of dead bacteria,<sup>16,17</sup> three forms of *H. pylori* are presently considered to exist, namely (in order of most to least virulent), the viable, culturable bacillary form, the VBNC coccoid form and the non-viable degenerative form.<sup>18–20</sup>

Morphologically, conversion from the bacillary to the coccoid form occurs through intermediate V- and U-forms<sup>13,14</sup> (Figs. 1 and 2), in which cell structures like the cytoplasm and cell membrane remain intact,<sup>15,21</sup> while the flagella tend to wrap around the coccoid cellular structure, thereby becoming near invisible. Other ultrastructural modifications to the coccoid form result in two sub-types. Type A has irregular edges with a rough surface and is considered to be a dead cell, while type B has a smoother surface, is smaller and is considered to be a living cell.<sup>21,22</sup>

In scanning electron microscope (SEM) analyses of the surface mucous gel layer of gastric cancer patients infected with *H. pylori*, Ogata et al.<sup>23</sup> observed the co-existence of both bacillary and coccoid forms. Other authors have confirmed the presence of the coccoid form in both the human stomach and duodenum,<sup>24–26</sup> although it seems that the percentage of coccoid forms is higher in the duodenum than in the stomach, to the point where only the coccoid form is

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