HHS Public Access

Author manuscript

Trends Microbiol. Author manuscript; available in PMC 2024 July 11.

Published in final edited form as:

Trends Microbiol. 2023 May ; 31(5): 453–467. doi:10.1016/j.tim.2022.10.007.

Bacterial chemotaxis in human diseases

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Abstract

To infect and cause disease, bacterial pathogens must localize to specific regions of the host where they possess the metabolic and defensive acumen for survival. Motile flagellated pathogens exercise control over their localization through chemotaxis to direct motility based on the landscape of exogenous nutrients, toxins, and molecular cues sensed within the host. Here, we review advances in understanding the roles chemotaxis plays in human diseases. Chemotaxis drives pathogen colonization to sites of inflammation and injury and mediates fitness advantages through accessing host-derived nutrients from damaged tissue. Injury tropism may worsen clinical outcomes through instigating chronic inflammation and subsequent cancer development. Inhibiting bacterial chemotactic systems could act synergistically with antibacterial medicines for more effective and specific eradication.

Keywords

Chemotaxis; bacterial pathogenesis; motility; chronic inflammation

Connections between bacterial chemotaxis and human diseases

Bacterial chemotaxis is a widely conserved sensory system of ancient evolutionary origin that facilitates directed flagellar-based motility based on exogenous physicochemical gradients [1] (see glossary). Through chemotaxis bacterial populations rapidly alter their localization, on the time-scale of seconds, to enhance survival through attraction to nutrients and repulsion from toxins [1]–[3]. Many bacteria that cause disease in humans, especially gastrointestinal pathogens, dedicate large portions of their genomes to chemosensory systems that facilitate chemotaxis [2]. Bacterial pathogenesis is often enhanced through sensing of environmental cues that leads to the coordinated expression of virulence regulons. It has been proposed that serious sequelae resulting from bacterial infection could be prevented by disrupting chemotaxis networks and motility [4]. However, the relationship between bacterial pathogenesis and chemotaxis is complex, and knowledge of the fitness advantages chemotaxis provides for microbes within hosts remains incomplete. To date,

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no antibacterial therapeutics are commercially available that act through the mechanism of inhibiting bacterial chemotactic machinery.

In this review we synthesize the current understanding of bacterial chemotaxis at the host-pathogen interface in relation to human diseases. We discuss how these findings implicate the importance of chemotaxis for success in inflamed tissue and how bacterial localization, driven by chemotaxis, may factor into clinical outcomes.

Fundamentals of bacterial chemotaxis

Bacterial chemotaxis is a longstanding model system for studying cellular sensory transduction and recent reviews have described the underlying biophysics [1], [5], [6]. Here, we focus on the clinical perspective and will summarize the molecular pathways of chemotaxis with brevity to provide the basics for readers to understand how bacteria localize in response to chemotactic stimuli (Fig. 1).

Chemotaxis imbues bacteria with the capability to localize, and relocalize, in response to chemical gradients, i.e. sources of chemicals. Chemical species that elicit chemotactic responses are referred to as chemoeffectors; chemicals that promote swimming up gradients are called chemoattractants and those that encourage swimming down gradients are called chemorepellents [1], [5]. Perception of chemoeffectors is facilitated by chemoreceptor proteins, which can directly bind chemoeffector ligands (Figure 1A) [7]. Chemoreceptors form trimers-of-dimers that further oligomerize into a large hexagonal lattice, known as a nanoarray, that serves to amplify ligand-sensing through highly-sensitive cooperativity [8], [9] (Fig. B,C). The chemoreceptor nanoarray complexes with the cytosolic histidine kinase chemotaxis protein A (CheA) and regulates its autophosphorylation based on chemoreceptor ligand occupancy. Phosphorylated CheA transfers the inorganic phosphate to chemotaxis protein Y (CheY). Phosphorylated CheY (CheY-Pi) can diffuse throughout the cell and directly bind the flagellar rotor to bias rotation, leading to changes in the direction of bacterial swimming. Chemorepellents elicit activation of this phosphorelay, raising CheY-Pi levels and increasing swimming reorientations, whereas chemoattractants inhibit phosphorylation and CheY-Pi production, leading to reduced swimming reorientations (Fig. 1D). Additional enzymes work in opposition to dephosphorylate CheA and CheY, and methyltransferases reversibly methylate chemoreceptors to dampen their signaling. These feedback pathways facilitate the logic necessary for adaptation to stimuli, enabling bacteria to either continue up or down chemoeffector gradients, or become desensitized to chemoeffectors [5].

Alongside sensing of exogenous stimuli via the canonical chemosensory pathway described above, bacteria integrate internal metabolic or energy status, i.e. energy-taxis, as well as redox-taxis and aerotaxis, into chemotactic behaviors [10]–[14]. We discuss these in further detail, and examples of their roles in virulence, in Box 1. Additionally, not all chemosensory pathways mediate chemotaxis (flagellum-mediated swimming motility), as some are involved in type-IV pili motility and control of secondary messengers [15].

From the perspective of a motile bacterial pathogen, the environment of the human host is a dynamic landscape of complex overlapping chemoeffector gradients frequently perturbed

by gut motility and hydrodynamic flow, nutrient influx, resident microbiota competitors, and inflammatory processes. Identifying what chemical species are chemoeffectors and measuring chemotactic behaviors of bacteria is non-trivial, and no single methodology or model system can fully recapitulate the circumstances in a human host (Fig. S1). An up-to-date compendium of purported chemoeffectors, with varying degrees of substantiation in terms of reproducibility, defined molecular mechanisms, and an established role *in vivo*, has been published [3]. Below, we focus our discussion on new and emerging evidence for the roles of chemoeffectors at the human host-pathogen interface for bacteria that pose substantial worldwide health burdens.

Chemotaxis systems of WHO priority pathogens

In 2017, the World Health Organization published its first list of antibiotic-resistant "priority pathogens" (WHO_{pp}) for which the development of new antimicrobial medicines is urgently required [16]. Based on factors such as severity of infections and lack of effective treatment options, species from 19 bacterial genera were identified that pose imminent threats to human health, 12 of which appear to possess chemotaxis-driven swimming motility [17, p. 3]. Of these, chemotaxis systems in *Shigella, Enterobacter, Morganella, Serratia, Proteus, Providencia,* and *Citrobacter* remain poorly understood, whereas chemotaxis in *Pseudomonas*, *Helicobacter*, *Escherichia*, *Salmonella*, and *Campylobacter* have been studied extensively. Consequently, we focus on these five genera as models to understand what roles chemotaxis plays in human infections and disease outcomes (Fig. 1A). WHO_{pp} that possess chemotaxis systems account for a significant number of deaths per year from infections or complications with underlying diseases such as cystic fibrosis (CF), environmental enteric dysfunction (EED), Guillain-Barré Syndrome (GBS), and chronic inflammation leading to the development of cancers (Fig. 2B–D). The latter include gastric cancer, bladder cancer, and colonic cancer, which are associated with infections by *Helicobacter* [18], *Escherichia* [19], and *Salmonella*/*Escherichia*/*Campylobacter* [20], [21], respectively (Fig. 2D).

Chemotaxis drives specific colonization topography based on chemoeffector gradients within the host [2]. However, the niche a pathogen colonizes is not static. Changes to chemoeffector gradients may occur due to aging, diet, or health. Pathogens themselves shape the human host environment as the infection proceeds through incubation, prodromal, illness, and chronic stages (Fig. 3) [22], [23]. These evolving circumstances pose discrete challenges and opportunities for motile chemotactic pathogens. Below, we discuss results from recent chemotaxis studies in this context to infer the ways in which chemotaxis provides fitness advantages for pathogens within the dynamic environment of the human host.

Roles for chemotaxis at different stages of infection

Initial colonization: incubation stage

Motility is a prerequisite for chemotaxis, so the magnitude of the role of chemotaxis for any infection stage relates to the prevalence of motile cells in the bacterial population (Fig. 3). A current paradigm is that the motile fraction decreases after initial colonization, presumably due to the high energetic costs of motility and chemotaxis [2], [24]. There is variability

amongst pathogens in this regard, perhaps owing to the challenges of colonizing certain host environments. For instance, *H. pylori* maintains motile populations long-term that migrate between stomach regions and seed colonization of new gastric glands [25]–[27]. In contrast, *P. aeruginosa* infections of the lung, and *C. jejuni* infection of the intestine, show strong shifts toward sessility through biofilm formation, and strains isolated from patients often show genes associated with motility and chemotaxis to be downregulated or lost [28]–[31]. Even if chemotaxis confers the greatest fitness advantages early in infection, thereafter even relatively small numbers of chemotactic cells imbue the bacterial population with the versatility to spread and relocate based on changing host circumstances (Fig. 3).

To colonize a naïve host, a pathogen often needs to outcompete native obligate fermenters of the microbiome within a mostly anaerobic environment (Fig. 3). To assist in this, WHO_{pp} chemotaxis systems interpret gradients of quorum-sensing molecules like indole [32] and autoinducer-2 [33] to regulate pathogen expansion and detect bacterial competitors (Fig. 3). In combination with chemoattraction to host-secreted factors such as urea [34] and mucin [35], chemotaxis drives pathogens from the lumen into contact with host tissue, to facilitate adherence and/or invasion of host cells [10], [36]–[38]. Roles of chemotaxis for pathogens colonizing naïve hosts is demonstrated by experiments with healthy conventional (i.e. intact microbiome) mammalian models inoculated with wildtype (WT) versus chemotactic-deficient strains. In such experiments *P. aeruginosa* [39], *H. pylori* [26], *C. jejuni* [40], *S. enterica* [38], and *E. coli* [41] show chemotaxis contributes to fitness and virulence in the range of 5–1000-fold. Notably, the roles of chemotaxis at early stages of infection are not captured *in toto* by experiments with gnotobiotic models, or animals pretreated with antibiotics to enhance pathogen colonization, because these systems have eliminated, or undermined, competition with the microbiome.

Briefly, we note there is variability amongst naïve host environments that may profoundly affect chemoeffector gradients, and thus, also, pathogen localization and colonization. One example is host age. The enteric pathogen *C. jejuni*, a prevalent cause of diarrhea in infants, exhibits chemoattraction to fucose derived from human breastmilk oligosaccharides, resulting in the expulsion of the pathogen into the feces of infants, where free fucose levels reach 4–5 mg/gram [42]–[45]. In this context breastmilk oligosaccharides ingested by infants confer protection against infection. In contrast, in the absence of dietary colostrum, *C. jejuni* scavenges fucose via gut microbiota that cleave mucins, such as *Bacteroides vulgatus,* resulting in increased *C. jejuni* colonization [46], [47]. This demonstrates the same chemotactic machinery operating in diverse host environments can lead to very different infection outcomes.

Post-inflammation: prodromal, illness, and chronic stages

As infection persists through prodromal and illness stages, inflammatory responses dramatically transform the host environment (Fig. 3) [23], [48]. Antibacterial processes perturb native microbiota, reactive oxygen and nitrogen species (RONS) are catalyzed by infiltrating phagocytes, and luminal oxygenation gradients are disrupted, permitting aerobic respiration (Fig. 3) [49]. Chemotaxis provides pathogen populations a means to capitalize on these new opportunities. Benefits from chemotaxis for pathogens beyond initial colonization

is demonstrated unequivocally by detailed examination of colonization and expansion over extended intervals. For example, a comparison of the spatial and temporal colonization dynamics of WT *H. pylori* and chemotaxis-null (Che$^-$) strains in mice showed chemotaxis is essential for spreading to new gastric glands over a 180 day period; a low inoculum (10^6 CFU) was sufficient for robust WT colonization of gastric mucus and glands within six days, whereas the Che$^-$ population collapsed [25], [50]. WT *H. pylori* exhibit "priority effects" and resist challenges from invaders, but chemotaxis-deficient strains are displaced [25], [26].

Animal dysbiosis models give further insight into how chemotaxis advances infection after initial colonization in which the host environment has become inflamed. The mouse colitis model is a widely-used system in which animals are primed with streptomycin that induces inflammation and disrupts the microbiota. In this host background competitive indices show *S. enterica* serovar Typhimurium to exhibit 10-fold greater fitness versus chemotaxis-null (Che$^-$) strains, or those with chemoreceptor deletions such as *tsr* and *aer* [51] or *mcpC* (4-fold) [38].

Much of the health burden of WHO_{pp} stems from pro-inflammatory colonization strategies in which pathogens instigate, and thrive, under conditions of severe inflammation (Fig. 2D). Studies with *S.* Typhimurium, *H. pylori*, and *P. aeruginosa* indicate motility and chemotaxis are among the mechanisms that drive aggressive inflammation responses [52]–[54], which can be counterproductive to pathogen eradication and cause lasting damage. One mechanism is through infiltrating phagocytes that disrupt the integrity of the epithelial barrier and cause tissue necrosis and bleeding [55] (Fig. 3). An emerging body of research reveals inflammation and host injuries present opportunities for pathogens to pirate host-derived nutrients [48], [51], [56]–[59] (Fig. 4). In particular, there is mounting evidence *H. pylori* induces gastric injuries through epithelial metaplasia to expand access to new stomach regions, and then preferentially colonizes injured tissue [60]. Experiments with gastric tissue injured by two-photon microscopy show *H. pylori* uses motility and chemotaxis to localize to lesions within minutes, with similar responses observed in injured organoid models [61], [62] (Fig. 4A,B, Movie S1).

One potential source of nutrients from damaged tissue is blood—rich in iron, amino acids, and sugars. Peptic ulcers caused by *H. pylori* are one of the most common sources of gastric bleeding and can result in anemia; when infection is cleared anemia can be alleviated [63], [64]. *H. pylori* can subsist on iron from blood hemoglobin *in vitro*, adheres to erythrocytes in capillaries of the lamina propria [65], [66], and reportedly exhibits chemoattraction to human blood plasma [67]. Bloody diarrhea is typical of infections by *S.* Typhimurium, *C. jejuni*, and enterohemorrhagic *E. coli* (EHEC), which may provide nutrients for expansion during colitis [68]–[70]. In the following section we consider the specific chemoattractant gradients present in inflamed and injured host tissue, including blood, that may aggravate inflammatory responses and contribute to chronic inflammation.

Chemoattractant gradients in diseases of chronic inflammation

Numerous metabolites and nutrients present in necrotic tissue and blood are sensed by WHO_{pp} chemotaxis systems as chemoattractants. We mapped results from a collection

of recent studies where small molecule chemoattractants present, or enriched, at sites of host injury are sensed through specific WHO_{pp} chemoreceptors (Fig. 4C). We restricted our analysis to the subset of purported chemoeffectors that have experimental structures determined of the protein-ligand complex or well-defined direct-sensing mechanisms. The resulting network of host-pathogen interactions, described below, suggests chemotaxis systems of WHO_{pp} are well-poised for opportunistic nutrient piracy at sites of injury.

Amino acids are released by damaged tissue, present at high concentrations in human serum, and serve as an excellent bacterial nutrient. For example, bacterial serine deaminases convert L-serine to pyruvate, effectively generating 15 ATP equivalents in a single enzymatic step. A striking number of WHO_{pp} chemoreceptors are dedicated to directly sensing amino acids as chemoattractants (Fig. 4C). A suite of new crystal structures of *Pseudomonas* chemotactic transducer (Pct) chemoreceptor proteins were captured in complex with a broad range of amino acids: PctA with Trp, Met, and Ile, PctB with Arg and Gln, PctC with γ-aminobutyric acid (GABA) [71]. A *pctABC* deletion mutant was unable to localize to scratch-wounded CF epithelial cells, suggesting a direct linkage between chemoattraction to amino acids and pathogenesis [37]. Structures of transducer-like protein (Tlp) 3 from *C. jejuni*, also known as *Campylobacter* chemoreceptor for multiple ligands (CcmL), show the ligand-binding domain complexed with isoleucine, alanine, valine, phenylalanine, leucine and other hydrophobic derivatives [72, p.], [73]. *C. jejuni* chemoreceptor Tlp10 senses aspartate and isoleucine as chemoattractants, among other ligands [74]. The Tsr and Tar chemoreceptors of Enterobacteriaceae mediate strong chemoattractant responses through direct sensing of Ser and Asp, respectively [2].

Sugars and other metabolites plentiful in human serum are perceived as chemoattractants by WHO_{pp} species (Fig. 4C). The Enterobacteriaceae chemoreceptor Trg facilitates chemoattraction to glucose and galactose, present in the blood at 5 mM and 5 μM, respectively [75], [76]. *C. jejuni* Tlp11 reportedly mediates chemoattraction to galactose and has thus been renamed as *Campylobacter* chemoreceptor for galactose (CcrG), and is associated with invasive isolates [77], and Tlp10 is involved in chemoattraction to fucose [74]. Serum urea levels are approximately 5 mM [78], which is a key host-derived molecule *H. pylori* utilizes as a substrate for urease to buffer against the acidic stomach environment. *H. pylori* chemoreceptor TlpB directly binds urea and mediates chemoattraction to sources as low as 50 nM [34], [79], and was demonstrated as a chemoattractant for injured tissue [61]. The structure of TlpC from *H. pylori* was captured in complex with lactate, a molecule present at millimolar concentrations in blood [80]. There has been substantial interest in the possibility that certain neurotransmitters are sensed as chemoattractants. A structure of such a complex was recently determined of *P. aeruginosa* chemoreceptor PctD bound with the eukaryotic signaling molecule acetylcholine, an integral inflammation signal that recruits T-cells to sites of infection [81], [82].

RONS catalyzed by phagocytes during inflammation have now been shown to serve important roles in directing bacterial localization (Fig. 4C). Despite the ability of neutrophils and macrophages to catalyze millimolar microgradients of antimicrobial oxidants like hypochlorous acid (HOCl) and peroxynitrite ($ONOO^-$), bacterial pathogens utilize robust antioxidant enzymes to eliminate RONS and persist [83]–[85]. These host-generated

oxidants can also supply inadvertent metabolic advantages for pathogenic bacteria. HOCl and $ONOO^-$ form tetrathionate and nitrate, which facultative anaerobes possessing nitrate- and tetrathionate-reductases, respectively, can use as terminal electron acceptors to outcompete native obligate anaerobes, as exemplified by *S.* Typhimurium and *E. coli* [10], [48], [51] (Fig. 4). *P. aeruginosa* McpN represents the first example of a chemoreceptor sensing nitrate directly [86] (Fig. 1A, Fig. 4C).

The question of whether human pathogenic bacteria directly sense RONS as chemoeffectors, and whether that elicits chemoattraction or chemorepulsion, remains an area of active investigation [11], [50], [85], [87]–[89]. A putative HOCl-sensing chemoreceptor was first identified in *H. pylori* [85], and homologous proteins have been shown to be present in *Salmonella*, *Campylobacter*, *Citrobacter*, and other bacteria that cause disease in humans [88]. Real-time video microscopy of *H. pylori* shows rapid chemoattraction to HOCl sources *in vitro*, dependent upon chemoreceptor TlpD [85] (Fig. 4D, Movie S2). TlpD signaling is regulated through its chemoreceptor zinc-binding (CZB) domain, which mediates responses to HOCl through direct oxidation of a conserved zinc-cysteine redox switch [85], [88], [89]. The fraction of gastric glands colonized by *H. pylori* is decreased by about half for mice lacking phagocyte oxidase, which catalyzes $O_2^{-\cdot}$ and H_2O_2, precursors for HOCl generation by neutrophil myeloperoxidase [50]. More generally, bacteria may utilize CZBs to regulate chemotaxis based on cellular processes and stimuli that alter Zn^{2+} homeostasis, which could explain reports of responses to diverse stimuli such as H_2O_2, $O_2^{-\cdot}$, metals, and exogenous nutrients [88].

In summary, some intriguing evidence supports the notion chemotaxis mediates a sort of bacterial “vampirism” for advantages in late stages of infection. Spirochetes are one system in which chemoattraction responses to serum, and serum as a pathogen nutrient source, are well-documented—*Borrelia burgdorferi* and *Treponema denticola* exhibit chemoattraction to serum, and *Leptospira interrogans* toward hemoglobin [90], [91]. Chemoattraction to inflamed and damaged tissue, and potentially to human blood sources, could underly why certain pathogens aggregate at sites of injury and impair recovery [60], [62], [90], [91]. We note there are some components of human serum reported as chemorepellents [74], but our literature search did not reveal any examples of WHO_{pp} chemorepulsion away from serum. Future investigations into the relationship of chemoattraction and host injury could provide important insights into the circumstances in which infections resolve or manifest into diseases of chronic inflammation (see Outstanding Questions Box).

Concluding Remarks

Is omeprazole a proof-of-concept chemotaxis-inhibiting therapeutic?

Antibacterial medicines generally act through inhibiting pathways essential for bacterial survival such as synthesis of cell walls, proteins, and nucleic acids. As discussed in the sections above, chemotaxis confers fitness advantages for bacteria within hosts, but is not essential for colonization and many pathogens lack chemotaxis systems altogether [2], [15]. Moreover, early stages of infection, when motility and chemotaxis is most utilized by pathogens, may not be a feasible window of opportunity for therapeutic intervention. So, are there clinical contexts that would justify designing new therapeutics that function

through inhibiting bacterial chemotaxis? The proton pump inhibitor (PPI) drug omeprazole, a WHO Essential Medicine used in the treatment of *H. pylori* infection, could represent a proof-of-principle application of such a strategy (Fig. 5).

Humans are one of only a few animals, and the only primates, that maintain a highly acidic stomach (pH 1.5–3.5), which is facilitated by parietal cells in the corpus gastric glands that secrete hydrochloric acid into the stomach lumen [92], [93]. The chemotaxis system of *H. pylori* is highly attuned to pH and multiple chemoreceptors coordinate to navigate the bacterium away from the deleterious acidic lumen toward the near-neutral mucosal lining and glands [94] (Fig. 5A). *H. pylori* exhibits antrum-dominant localization during initial colonization, a region of the stomach lacking parietal cells [26], [34], [94]–[96]. As infection persists, the bacterium inhibits parietal cell H^+/K^+ ATPase pumps that drive proton secretion through its type IV secretion system (T4SS) virulence factors, and other mechanisms, and spreads to the corpus and fundus [34], [94], [96]. Hence, the initial colonization, and subsequent expansion of *H. pylori* in the stomach, driven by chemotaxis, reflects avoidance of parietal cell-generated acid gradients [94] (Fig. 5).

In the 1990s the MACH1 and MACH2 clinical studies showed omeprazole boosted *H. pylori* eradication rates of combinatorial therapies of amoxicillin+clarithromycin from 25 to 95%, and metronidazole+clarithromycin from 72 to 91%, compared to a 1% elimination rate for omeprazole alone [97], [98]. Omeprazole upends the natural pH gradients of the stomach by inhibiting parietal cell H^+/K^+ ATPases, as well as sensitizes the bacteria to acid, and may increase the activity of pH-sensitive antibacterials [97]–[99]. Alongside these effects, the disrupted chemoeffector gradients induce a profound shift in the topography of *H. pylori* colonization, encouraging the bacteria to expand through chemotaxis to the glands and mucus of the corpus and fundus [94], [96], [100] (Fig. 5B). Some evidence links the dramatic PPI-driven disorientation of *H. pylori* to synergy with antibacterials [94], [101]. The inhibition of parietal cell function is short-lived and gastric pH resets within 24 hours after omeprazole treatment [101], [102]. Pulsed omeprazole administrations alone reduced bacterial load by 95% [101]. Thus, luring the bacteria to a temporarily neutral pH oasis, only to then regenerate the native bactericidal HCl gradients, may leave the bacteria stranded in an inhospitable niche and predispose them to elimination by antibacterial agents. Altered pH gradients could also encourage the bacteria to vacate sites of injury, thereby helping heal tissue.

Summary and outlook

The chemotactic portion of pathogen populations enable colonization of suitable niches early in infection and expansion to other suitable niches at later infection stages. Next-generation antimicrobials may benefit from adopting multifaceted strategies that better incorporate knowledge of the diversity of pathogen lifestyles within hosts [103]. The example of omeprazole suggests disorienting chemotactic pathogens can act synergistically with antibacterial therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Glossary

CF	cystic fibrosis, an inherited disorder affecting the lungs.
CheA	histidine kinase chemotaxis protein A, a histidine kinase involved in relaying chemotactic signals.
chemotaxis	directed flagellar-based motility toward and away from chemical gradients.
chemoeffector	a chemical that elicits a chemotactic response from bacteria.
chemoattractant	a chemical that elicits attraction mediated through chemotaxis.
chemorepellent	a chemical that elicits repulsion mediated through chemotaxis.
CheY	chemotaxis protein Y, the cellular phosphorylation status of CheY influences flagellar rotation.
CZB domain	chemoreceptor zinc-binding domain, a sensory protein domain implicated in HOCl-sensing.
RONS	reactive oxygen and nitrogen species, bactericidal oxidants catalyzed by the host immune system.
Tlp	transducer-like protein, the historical name of chemoreceptors in some species like *Helicobacter* and *Campylobacter*.

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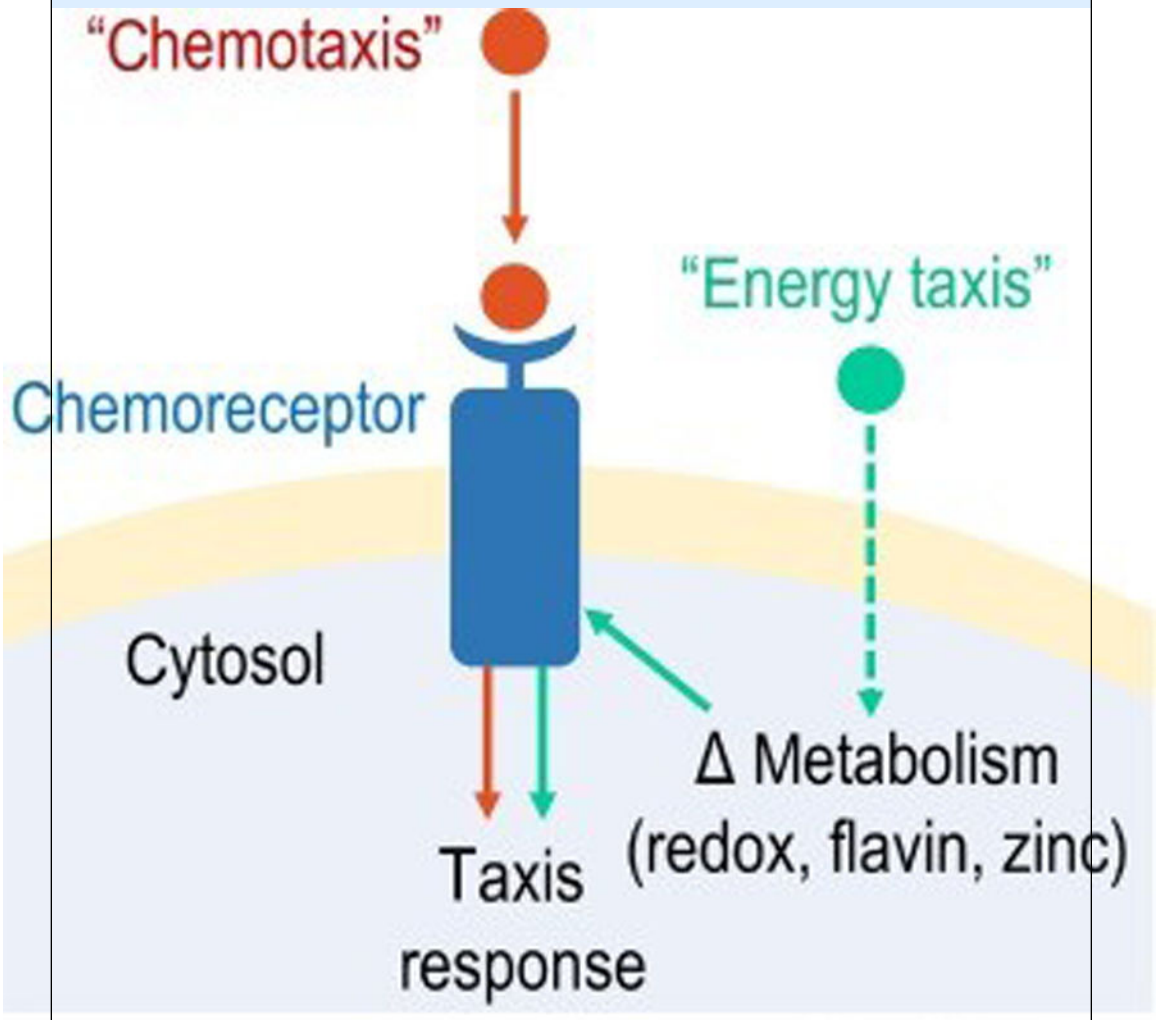
Box 1



Diversity of bacterial taxis behaviors

Bacteria exhibit a wide range of taxis behaviors across biology whereby bacterial populations control localization through stimuli that trigger swimming reorientations (see Figure 1 in main text). In this review we have used 'chemotaxis' as an umbrella term for these collective phenomena and to keep the concepts herein approachable to non-experts. However, the field utilizes more precise terminology to distinguish taxis behaviors based on mechanism and the type and source of stimuli. Bacterial swimming behaviors can be influenced by gravity (geotaxis), light (phototaxis), magnetic fields (magnetotaxis), fluid current (rheotaxis), pH conditions (pH taxis), temperature (thermotaxis), osmolarity (osmotaxis), oxygen concentrations (aerotaxis), redox potentials (energy taxis or redox taxis), and forces in vortices (gyrotaxis) [110]. The distinction between the mechanisms of chemotaxis and energy taxis is that the former relates to direct recognition of the chemoeffector ligand, typically originating from an exogenous source, whereas the latter relates to sensing internal metabolic changes induced by stimuli, such as through changes to pools of flavin redox potentials or zinc homeostasis (Figure I) [15].

Cases exist where a taxis behavior may fall into more than one of the aforementioned categories, or stimuli may elicit multiple taxis behaviors. An exemplar is the family of aerotaxis chemoreceptors (Aer), which are well documented as playing important roles in pathogenicity. Some Aer chemoreceptors mediate aerotaxis through direct sensing of O2 via heme [111,112], and others perform energy taxis by monitoring flavin adenine dinucleotide oxidoreduction [113]. S. enterica uses Aer and energy taxis for attraction to host-derived nitrate, which contributes to invasion of Peyer's patches [11].

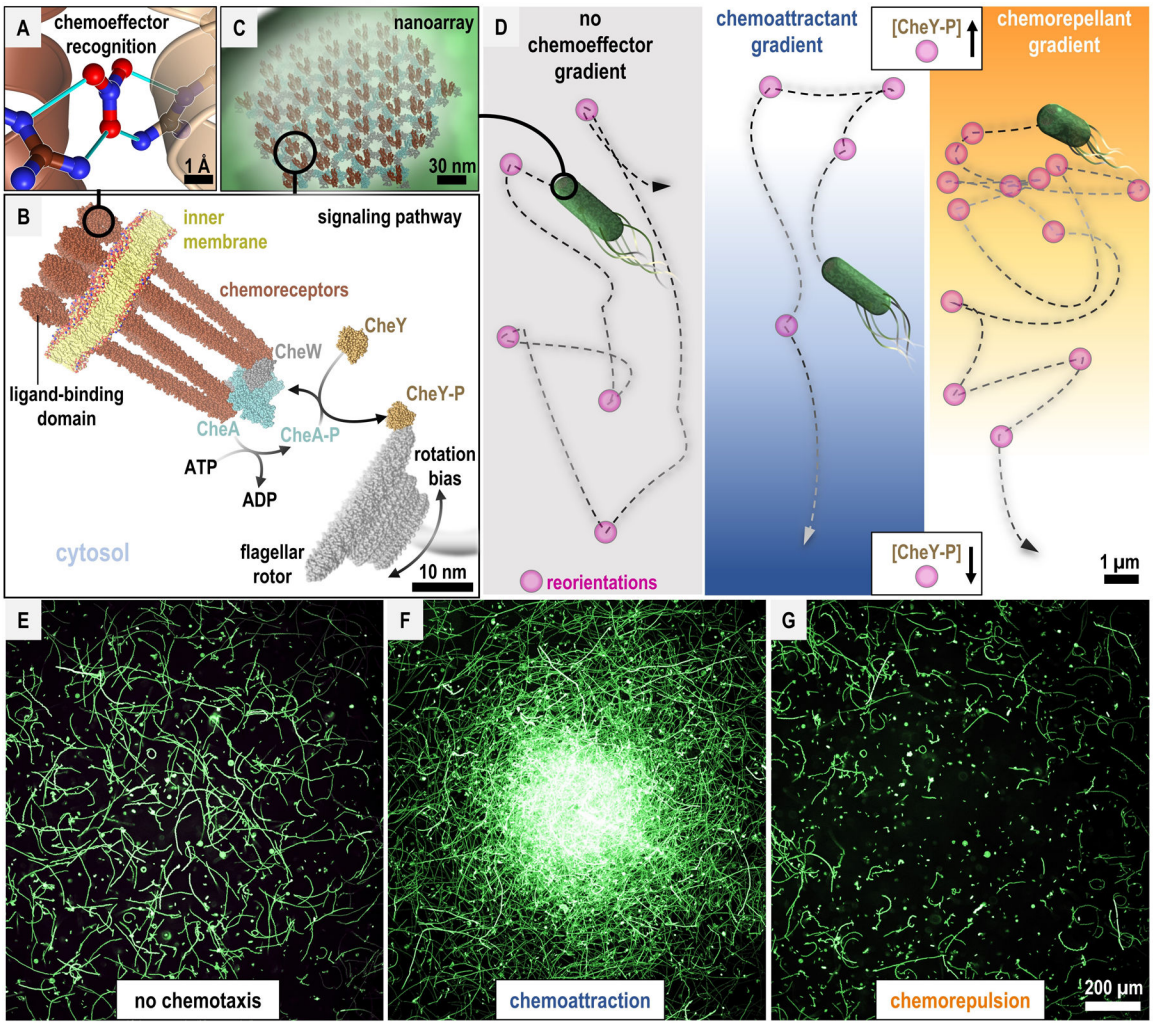


Fig. 1. Bacterial chemotaxis across atomic, molecular, cellular, and population scales.

A. Chemoreceptors can recognize chemoeffectors through direct binding. McpN from *Pseudomonas aeruginosa* is shown binding nitrate at the interface between two chemoreceptor monomers (dark and light brown, PDB 6gcv [86]). Hydrogen bonds between the proteins and nitrate ligand are shown as cyan lines. B. Chemoreceptor core signaling unit [8], [104] and the canonical phosphorelay of bacterial chemotaxis. Distance between the chemoreceptor complex and flagellar rotor not to scale. C. Chemoreceptor nanoarrays amplify chemoeffector sensing [8], [104]. D. Bacterial swimming and reorientation bias in chemoeffector gradients. Hypothetical bacterium swimming trajectories are depicted as dashed lines. E-G. Chemotactic responses by motile bacterial populations absent chemoeffector, or to central sources of chemoattractant or chemorepellent. Size bars are indicated. See Figure S1 for *in vitro* methods of measuring chemotactic responses at the atomic, molecular, cellular, and population scales.

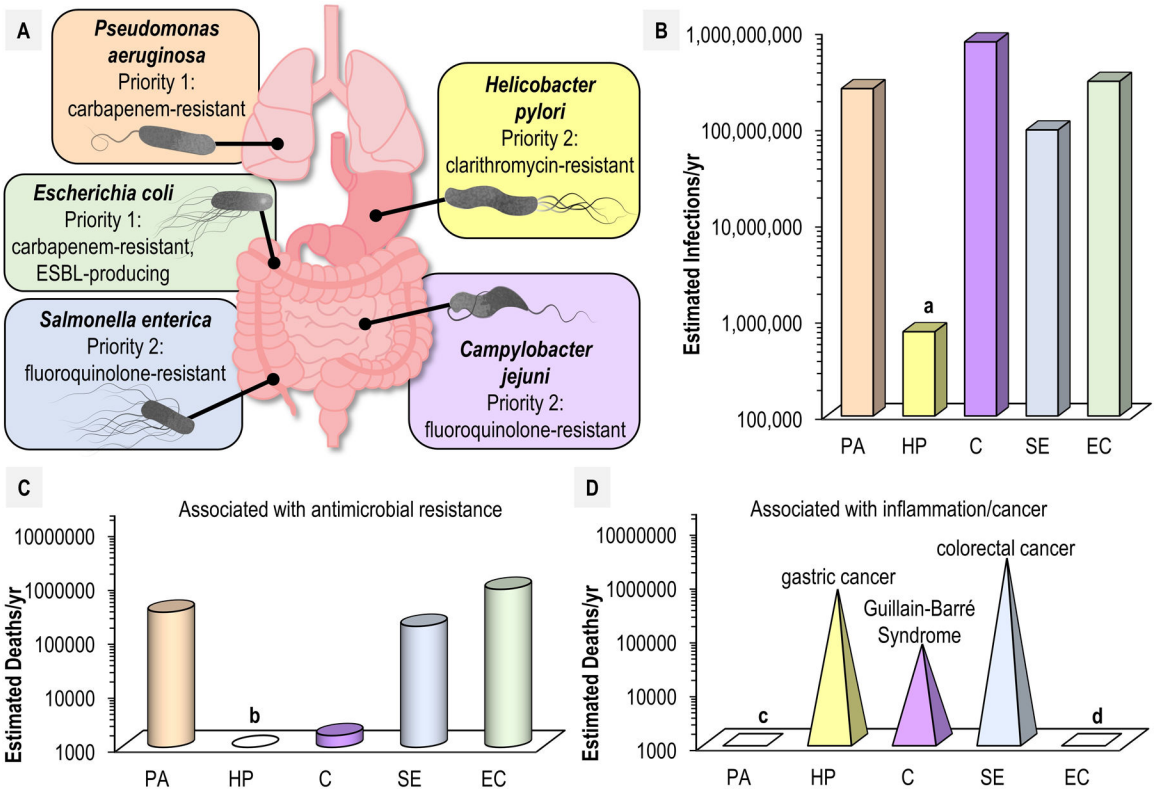


Fig. 2. Disease and mortality associated with chemotactic WHO$_{pp}$.

A. Typical infection sites associated with human disease for select chemotactic pathogens are indicated, along with their priority designation by WHO. B. Estimated annual infections worldwide by pathogen: PA; *Pseudomonas aeruginosa*, HP; *Helicobacter pylori*, C; *Campylobacter* spp., SE; *Salmonella enterica* (all serovars), EC; *Escherichia coli*. Estimate of *H. pylori* annual infections is based on that the bacteria infect approximately half of the world's total population (a). C. Annual deaths associated with antimicrobial resistance worldwide. Estimates based on data from [105]. *H. pylori* is not typically associated with deaths from acute infection and so is omitted (b). D. Speculative estimates for deaths associated with select diseases of inflammation and cancer are shown. Estimates are based on risk factors associated with bacterial infections based on available data: "Antibiotic Resistance Threats in the United States" https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf, "WHO publishes list of bacteria for which new antibiotics are urgently needed" https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed, "Population-based Prospective Study of the Combined Influence of Cigarette Smoking and Helicobacter pylori Infection on Gastric Cancer Incidence: The Hisayama Study" https://academic.oup.com/aje/article/168/12/1409/155955, "Guillain-Barré Syndrome" https://www.cdc.gov/campylobacter/guillain-barre.html, and [106]. *P. aeruginosa* and *E. coli* are agents suspected to instigate diseases of chronic inflammation and cancers, but we did not identify literature describing specific risk factors associated with these diseases (c, d).

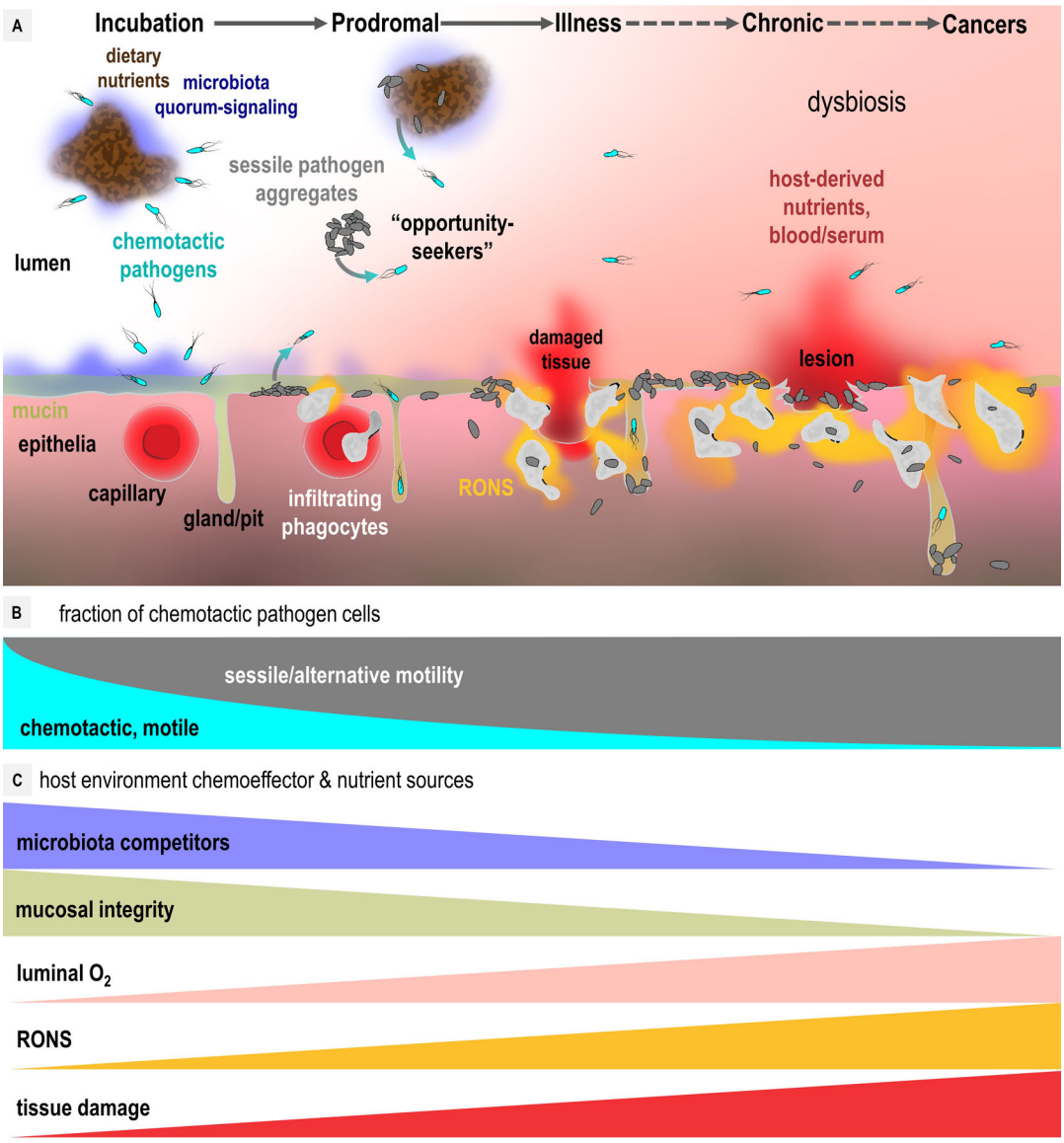


Fig. 3. Evolution of chemoeffector gradients during disease progression.

A. A generalized model of the host environment during infection. Chemotactic pathogens (cyan cells) localize to nutrient sources and host tissue. After initial colonization pathogens shift toward sessility (gray cells), with some cells departing aggregates and biofilms to act as chemotactic "opportunity seekers" to colonize new regions (gray to cyan arrows). Host inflammatory responses and RONS generation (orange) can result in tissue damage (red) through phagocyte transmigration, and disrupt luminal O_2 gradients (pink). Most infections resolve, but some may progress to chronic or cancerous stages (dashed lines). B. Motile and chemotactic versus sessile fraction of pathogen populations as a function of disease progression. C. Gradients of chemoeffectors, nutrients, and toxins relevant to pathogen colonization as a function of disease progression.

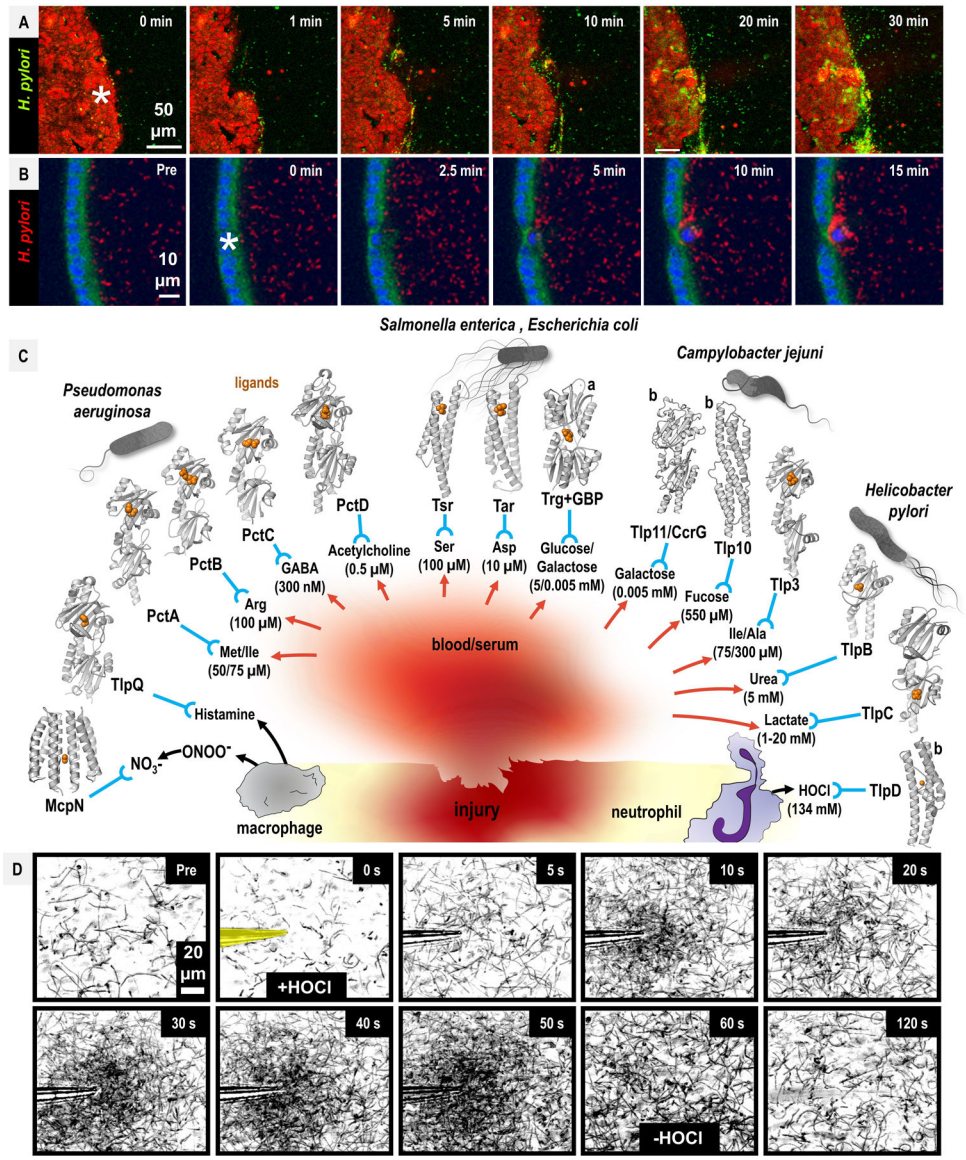


Fig. 4. Pathogen chemoattraction to sites of host injury.

A-B. *H. pylori* exhibits chemoattraction to injured murine gastric tissue (A), and with murine gastric organoids (B). Injury was induced through single-cell photo-damage (asterisks). See also Movie S1 for the full video. Data from [61], [62], used with permission.

C. Chemoattractants present at sites of injury and in human serum. The concentration of chemoattractants in blood/serum (red arrows), or produced through phagocyte oxidants (black arrows) are noted in parentheses, and the chemoreceptors involved in direct binding and sensing of the chemoattractants (blue) are indicated. Structures of chemoreceptor ligand-binding domains are shown for select WHO_{pp}, with chemoeffector ligands in orange. For most of the interactions depicted it is unknown whether the presence of the chemoattractant within serum/damaged tissue mediates injury tropism. Trg senses glucose and galactose through galactose-binding protein (GBP); the structure shown is for GBP bound to galactose, denoted with “a.” Alphafold2 models are shown for Tlp11/CcrG

and Tlp10 from *C. jejuni*, and TlpD from *H. pylori*, denoted with "b." Chemoeffector concentrations are indicated. D. *H. pylori* chemoattraction to HOCl *in vitro*. A time-course of *H. pylori* chemotactic responses to the neutrophilic oxidant HOCl is shown pre-treatment (Pre) and at indicated timepoints. At time 0 s, a micropipette containing buffered 10 mM HOCl is inserted (yellow), and the motile bacteria in the field of view accumulate. At 60 s the HOCl source is removed and the bacteria disperse. Panels represent min-projections of 0.5 s at each time point. Data from [85], used with permission. See also Movie S2 for the full video.

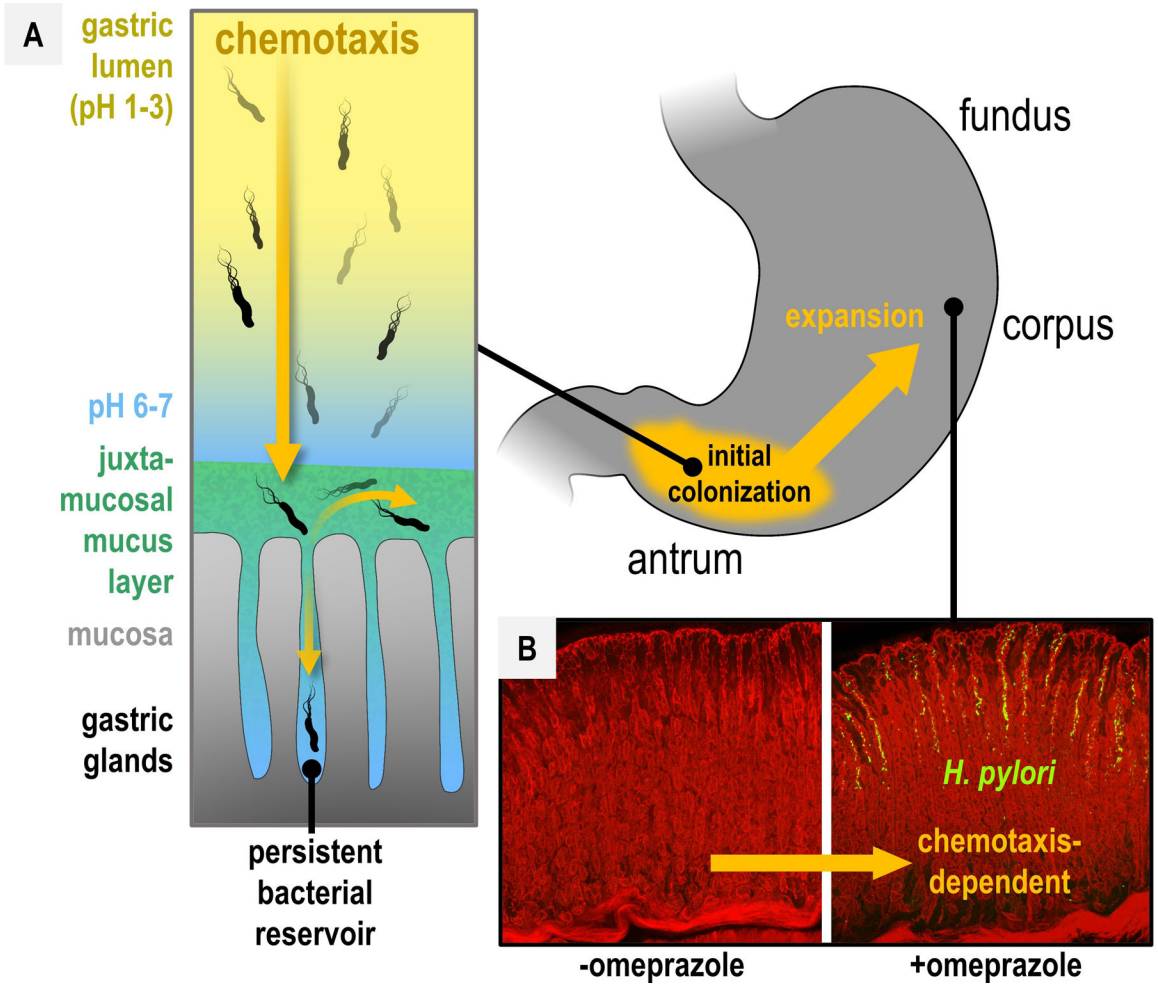


Fig. 5. Impact of omeprazole on *H. pylori* chemotaxis and colonization topography.

A. Chemotaxis-dependent localization is indicated by orange arrows. Chemotactic sensing of gastric pH gradients (yellow to blue) guides *H. pylori* to the neutral juxtamucosal mucus layer (green). Through chemotaxis, *H. pylori* invades gastric glands and establishes persistent bacterial reservoirs that seed expansion to new glands [26]. B. Omeprazole treatment inhibits parietal cell acid secretion in the corpus, enabling the bacteria to expand through chemotaxis to the corpus glands. Data from [94], used with permission.