P-ISSN: 2410-8863
E-ISSN:2958-6178
https://djvs.uodiyala.edu.iq
Pages:165-191

Diyala Journal for Veterinary Sciences
Vol. 4 No.3 September (2026)

https://doi.org/10.71375/djvs.2026.043012

Arcobacter butzleri: A review

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Important dates: **Received:** 23-July-2026; **Accepted:** 26- August-2026; **Published**: September-2026

Abstract:

Arcobacter butzleri classified as *Aliarcobacter butzleri* under the revised taxonomy has emerged as an important zoonotic foodborne and waterborne pathogen associated with gastrointestinal infections, bacteremia, septicemia, and other extraintestinal diseases in humans, as well as enteritis, abortion, and reproductive disorders in livestock, particularly cattle, sheep, and pigs. Significant strides have been made in comprehending its taxonomy, epidemiology, genetic variation, as well as pathogenic capability since it was identified as an emerging pathogen. Advances in whole-genome sequencing and comparative genomic analyses have significantly improved the characterization of virulence-associated genes and clarified its taxonomic position within the family Arcobacteraceae. Nevertheless, many aspects of its interaction with the host immune system and the mechanisms responsible for disease development remain poorly understood. Therefore, this review provides a comprehensive and updated overview of the current knowledge regarding the taxonomy, pathogenicity, virulence determinants, antimicrobial resistance, and host–pathogen interactions of *A. butzleri*, with particular emphasis on its immunopathogenesis. Recent evidence concerning antimicrobial resistance, including the multidrug-resistant (MDR) potential of A. butzleri, is also considered. In addition, recent findings on innate immune responses, inflammatory mediators, immune modulation, and current knowledge gaps are critically discussed to their potential implications for improving the diagnosis, prevention, and control of *A. butzleri* infections.

Keyword: *Arcobacter butzleri*, immunopathogenesis, cytokines, MDR

Introduction

Arcobacter has become an important foodborne zoonotic pathogen, causing severe infections in humans and animals (Chieffi *et al*., 2020). Arcobacters are present in a wide range of ecological niches, but their high prevalence in a variety of food products and water sources poses a risk to

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human health (de Alegría Puig *et al.*, 2021). When it comes to human Arcobacteraceae, *A. butzleri* with *A.cryaerophilus* are the most often found species that cause enteritis (de Alegría Puig *et al.*, 2023; Martinez-Malaxetxebarria *et al*., 2022). Furthermore, *A. skirrowii*, *A. lanthieri*, and *A. mytili* have all been associated with rare instances of human infections (Kerkhof *et al.*, 2021; Vasiljevic *et al.*, 2019).

Increasing evidence for the role of *A. butzleri* in human gastroenteritis, chronic diarrhea, bacteremia and extraintestinal infections focused more research on this organism in humans, especially patients with compromised immune defenses. The international commission on microbiological standards for foods (ICMSF) classifies *A. butzleri* as a health hazard since the zoonotic character of this species allows its transmission from animals to humans and, consequently, its contact with animal-based foods. This organism has a broad spread and potential transmission to humans via raw milk, vegetables, poultry and pigs from contaminated water thus stresses importance in terms of food safety as well as a healthy environment (Collado & Figueras, 2011; Zhou *et al.*, 2023).

Like various common intestinal bacteria, *A. butzleri* has an exceedingly flexible relationship with its environment. Genetic research found that it possesses plenty of genes that assist in stress management, nutrient utilization, preservation in varied environmental conditions and dependability to oxygen deprivation. These characteristics make it easier for the pathogen to remain in water systems, food processing areas, and biofilms for an extended period of time, which increases the likelihood of transmission from one host to another. It is more likely that pathogenicity was caused by the combined effects of numerous virulence factors than by a single dominant toxin, since whole-genome sequencing has also revealed a broad spectrum from putative virulent -associated genes responsible for attachment, invasion, cell death, acquisition of iron, and immune suppression (Yang *et al*., 2019).

Although the virulence potential of *A. butzleri* is increasingly recognized, the development and heterogeneity of host immune evasion strategies employed by *A. butzleri* to establish infection in mammals remain poorly understood. Infection, according to experiments, activates epithelial cells, brings in innate immune cells, and causes the creation of chemokines and cytokines that promote inflammation (Chieffi *et al*., 2020; Isidro *et al.*, 2020). It appears that the bacterium can activate intracellular inflammatory cascades like NF-κB and MAPK via boosting pattern-recognition receptor

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signaling, especially Toll-like receptor-mediated pathways. Still, there are a lot of unanswered questions about how adaptive immunity is controlled, how the immune system avoids detection, and what factors in the immune system contribute to the severity of diseases.

Aiming to elicit the immune response elicited by this bacterium, this review highlights adaptive and natural immunological responses, mediators of inflammation, and virulent factors that contribute to activated immunity with evasion. It also identifies current knowledge deficiencies that should guide future experimental with innovative studies, which is important given rising reported proof linking *A. butzleri* to humans illnesses and the growing interest in host pathogen interactions.

Taxonomic Classification

After being reclassified as *Arcobacter cryaerophilus* and *Arcobacter nitrofigilis*, respectively, two aerotolerant species that had been previously placed in the genus Campylobacter were transferred to the new genus Arcobacter in 1991by (Vandamme *et al*., 1991). This was followed shortly after by the addition of the newly described species *Arcobacter skirrowii* to the genus Arcobacter, which was previously known as *Campylobacter butzleri*. These taxonomic revisions reflected the unique genetic and phenotypic features that distinguish Arcobacter from other Campylobacteraceae (Pérez-Cataluña *et al.*, 2019). In 1992, (Vandamme *et al.*, 1992) who reclassified *Campylobacter butzleri* as *A.butzleri* and described a new species, *A. skirrowii*. *C.butzleri* had been previously isolated from humans and animals suffering from diarrhea (Kiehlbauch *et al.,* 1991) , while A. *skirrowii* had been collected from the feces of lambs suffering from diarrhea, as well as from aborted pig, ovine, and bovine fetuses, as well as from the prepuce of bulls.

Our knowledge of the genus's evolutionary relationships was greatly enhanced by subsequent developments in molecular typing methods, such as AFLP, sequence-based studies, and restriction fragment length polymorphisms (RFLP). Subsequent molecular evidence suggested that the two populations originally thought to make up *A. cryaerophilus* should be considered a single species, rather than two different taxa(Mahapatra, 2026).

An increase in the number of known species of *Arcobacter* occurred after the description of several new species, such as *A. cibarius, A. halophilus*, *A. mytili*, *A. thereius*, *A. marinus*, *A.*

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trophiarum, *A. defluvii*, and *A. molluscorum*, were published. The outcomes demonstrated the remarkable biological diversity within the species and its ability to colonize many environments, such as those associated with foods, water, and healthcare facilities (Chieffi *et al*., 2020).

Recent advances in whole genome phylogenetic research and *16S rRNA* gene sequences have greatly enhanced Arcobacter classification. According to some environmental sequences that have been made public, there are more species that have not been reported or that have not been grown. This means that there is more variety in the genus than what is currently known. The transition from phenotype-based classification to genome-based taxonomy has therefore provided a more robust framework for understanding the evolutionary relationships, ecological distribution, and clinical significance of *Arcobacter* species.

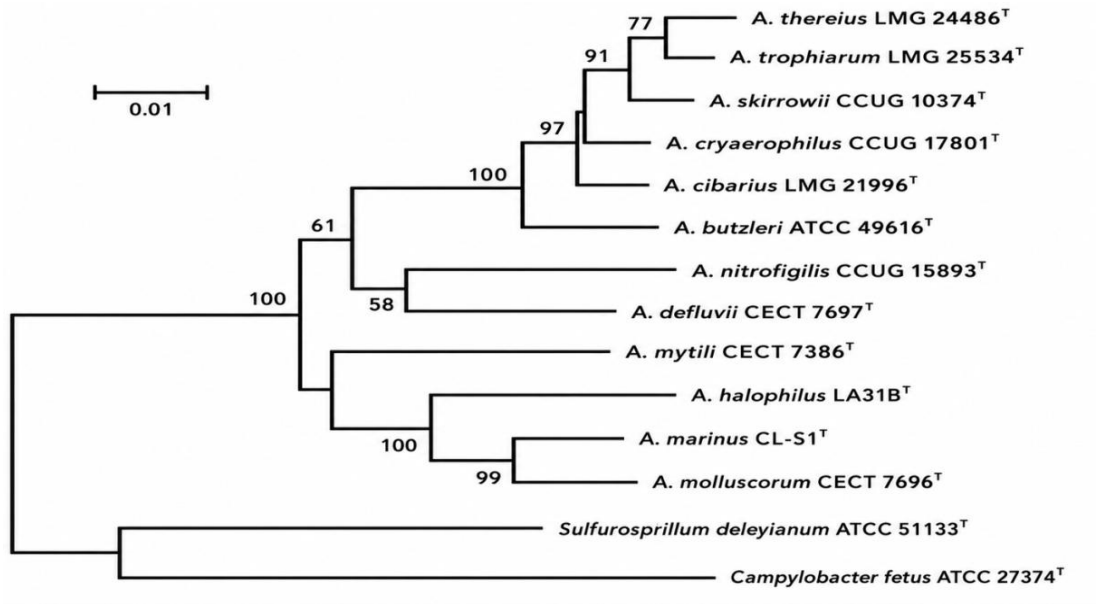

Figure 1 : Phylogenetic analysis of the *16S rRNA* gene revealed that sequence similarity among the twelve described Arcobacter species varied between 92.1% and 98.9%. The closest relationship was identified between *A. cibarius* and *A. cryaerophilus*, while *A. thereius* and *A. halophilus* exhibited the greatest genetic divergence (Collado & Figueras, 2011).

Pathogenicity of *Arcobacter*

The pathogenic potential of Arcobacter species has been increasingly recognized following the availability of whole-genome sequencing data, particularly for *A. butzleri*. By using genomic analyses, a number of putative virulence-associated genes have been identified that are believed to be

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involved in bacterial colonization or invasion, persistence in tissues and damage to host tissue (Zambri *et al*., 2019). *CadF, cj1349, ciaB, mviN, pldA, tlyA, hecA, hecB* and *irgA* are some of the most widely studied as they show high homology with virulence factors described for other pathogenic bacteria (eg. *Campylobacter jejuni; Vibrio cholerae* and pathogenic *Escherichia coli*)(Ghaju Shrestha *et al.*, 2022).

A. butzleri likely employs a multipronged approach to disease, according to the expected roles of these genes. As the initial stage of host colonization, the adhesins CadF and Cj1349 enable the bacteria to adhere to the fibronectin present on intestinal epithelial cells(Khan *et al.*, 2024). While PldA's phospholipase activity and TlyA's hemolytic activities cause damage to host cells, the invasion-associated protein CiaB facilitates bacterial entrance into epithelial cells. Although the exact biological roles of other factors like HecA, HecB, MviN, and IrgA are not fully understood, it is thought that they contribute to adhesion, iron uptake, survival in adverse environments, and modification virulent of bacteria (Ferreira *et al.*, 2016).

Besides the important roles of each of these virulence-related factors, the pathogenesis of *A. butzleri* is a progressive process that begins with intestinal colonization, progresses through epithelial invasion, and culminates in disruption of the intestinal barrier and activation of the host immune response (Figure 2). Adhesion and colonization of the intestinal mucosa, along with bacterial invasion and the activity of cytotoxic factors, can damage epithelial cells and their membranes. Claudins are key structural proteins for tight junctions, and claudin protein rearrangement can lead to intercellular permeability with consequent weakening of the integrity of the intestinal epithelial barrier(de Alegría Puig *et al.*, 2023).

Pattern recognition receptors, such as TLR2, TLR4, and TLR5, can recognize bacterial components, activating endogenous cellular signaling pathways, including MyD88, NF-κB, and MAPK. This type of signaling stimulates the synthesis of inflammatory mediators such as IL-8 (CXCL8), IL-6, TNF-α, and IL-1β, along with chemokines such as CXCL1 and CXCL2, to help attract neutrophils, macrophages, and other immune cells to the intestinal tissue. This leads to an inflammatory response, epithelial damage, increased mucus secretion, oxidative stress, and loss of intestinal barrier integrity, which can cause enteritis or watery diarrhea. Furthermore, motility, iron

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acquisition, and biofilm formation can help the bacteria withstand harsh environmental conditions, increasing *A. butzleri's* infectiousness(de Alegría Puig *et al*., 2023).

Molecular screening has demonstrated that these virulence-associated genes are most frequently detected in *A. butzleri*, *A. cryaerophilus*, and *A. skirrowii*. Nevertheless, homologous genes have also been reported in several other *Arcobacter* species, indicating that virulence determinants are not restricted to a single species within the genus. Interestingly, experimental studies have shown that certain species lacking one or more of the classical virulence genes, such as *A. thereius* and *A. mytili*, retain the ability to adhere to and invade Caco-2 intestinal epithelial cells (de Alegría Puig *et al.*, 2023). These findings suggest that additional, as-yet-unidentified virulence mechanisms may contribute to pathogenicity. However, an unclear association between the presence of virulence genes and the pathogenicity associated with cell lines has been observed (Ferreira *et al.*, 2016). As all species of *Arcobacter* might not be pathogenic, such as nitrogen-fixing *A. nitrofigilis* (Levican *et al.*, 2013), more studies should be conducted regarding useful aspects, pathogenicity and virulence potentials of the *Arcobacter* species.

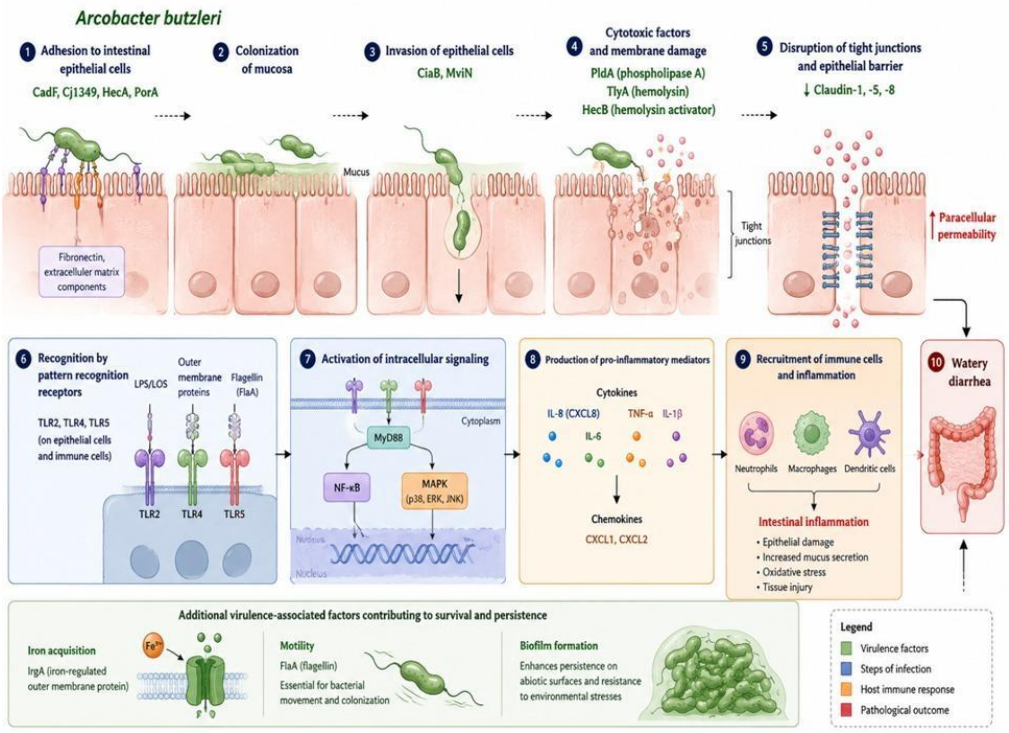

Figure 2: Proposed mechanism of *Arcobacter butzleri* pathogenesis and host immune activiation

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Virulence Factors (Chieffi *et al*., 2020)

- **Genomic Basis of Virulence Determinants**

Advances in whole-genome sequencing have substantially improved current knowledge of the virulence mechanisms of *Arcobacter butzleri*. Since the publication of the first complete genome sequence by Miller et al. (Miller *et al*., 2007), the increasing number of genome assemblies deposited in public databases has facilitated comprehensive comparative genomic analyses, enabling the identification of numerous virulence-associated genes (VAGs) involved in host colonization, persistence, and pathogenicity (Chuan *et al*., 2022).

The reference strain *A. butzleri* RM4018 possesses several genes homologous to virulence determinants previously characterized in *Campylobacter jejuni*. These include the fibronectin-binding proteins cadF and cj1349, the invasion-associated gene *ciaB*, the putative virulence factor mviN, the phospholipase *pldA*, and the hemolysin tlyA, all of which are considered major contributors to bacterial adhesion, invasion, and host cell damage.

Besides these conserved determinants, the RM4018 genome contains additional genes potentially associated with pathogenicity. These include *irgA*, encoding an iron-regulated outer membrane protein homologous to that described in *Vibrio cholerae*, where it contributes to iron acquisition and bacterial virulence. Homologous proteins have also been implicated in the pathogenicity of uropathogenic *Escherichia coli* (Isidro *et al*.2020). Other putative virulence determinants identified in the genome include *hecA*, which encodes a filamentous hemagglutinin involved in bacterial adhesion, hecB, encoding a hemolysin activation protein, and *iroE*, an enterobactin hydrolase previously reported in pathogenic *E. coli* strains (Miller *et al*., 2007).

Comparative genomic studies have subsequently expanded the repertoire of putative virulence genes in *A. butzleri*. A chromosomal locus including the *waaF* and *waaC* genes, which are involved in the manufacture of lipoligosaccharides , was found by Rovetto et al. Past research has linked these genes to bacterial virulence in *Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae*, and other Gram-negative bacteria (Fanelli *et al.*, 2019). While this genomic region remains intact among different *A. butzleri* strains, comparative investigations further indicated that its genetic architecture changes greatly among isolates. The incredible genomic diversity within this species is

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demonstrated by the presence of novel glycosyltransferase genes in certain strains that do not have orthologs in other genomes (Gabucci *et al*., 2023).

(Fanelli *et al*., 2019) Comparative genomics with five genomes of *A. butzleri* yielded additional virulence linked genes that play a role in bacteria pathogenicity. All of the analyzed isolates had certain traits in common, like the transcriptional regulator *virF,* which may be essential for regulating pathways linked to virulence. In comparison, virulence-associated locus *VirE* was found in only one strain suggesting that the virulence gene repertoire differs markedly between strains. While a conserved "core" set of virulence determinants are present, these demonstrate that the accessory genome contributes a high level of genetic diversity among *A. butzleri* isolates and therefore the potential for differing pathogenicity potential. Comparative genomics shows large numbers of virulence-associated genes in *A. butzleri*, some widely conserved and others strain-specific. Functional characterization as well as genome sequencing should continue to elucidate how these different factors contribute to colonization by bacteria, host adaptability, and progression of disease (Nadella *et al*., 2023).

Adhesion and Colonization Factors

A crucial initial stage in the pathogenesis of *A butzleri* is its adherence to the intestinal epithelium. Upon successful attachment, bacteria can establish colonies within the host's intestines, persist for a prolonged duration, and ultimately penetrate the host's tissues. Genomic comparisons show that several *A. butzleri* adhesion-related genes are similar to pathogenic *C. jejuni* factors (Uljanovas *et al.*, 2023).

Extracellular matrix proteins on intestinal epithelial cells bind to bacterial adhesion proteins, such as CadF and fibronectin-binding proteins Cj1349. These proteins can bind to fibronectin, allowing bacteria to access the host cell surface and thus initiate infection and colonization (Gonzalez-Morales *et al.*, 2026). Despite the source of isolation and geographical location dependent prevalence, molecular epidemiological studies demonstrate that these adhesion-associated genes are widely distributed in *A. butzleri* isolates (Chuan *et al.*, 2022). Based on the study by (Douidah *et al.*, 2012), *A. butzleri* isolates from humans and animals carried virulence determinants, including key adhesion genes which utilized a PCR test to target nine virulent associated genes. In another study conducted

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by (Tabatabaei *et al.*, 2014) in study 113 *A. butzleri* isolates of diverse codon type were analyzed and it was suggested that the virulence genes *cadF* and *cj1349* found to be present in all *A. butzleri* isolates from most locations in southern Iran now known as the "core" genes. This suggests that these genes are included on the conserved virulence repertoire for this species.

On the other hand, research done in different parts of the world has shown that gene distribution is more variable. The fact that *A. butzleri* isolates generated from shellfish had reduced frequencies of various adhesion associated genes suggests that biological niches and environmental factors may impact the virulence gene profile, as pointed out by (Gonzalez-Morales *et al*., 2026). Also, there was a lot of variation in the distribution of adhesion determinants; for example (Whiteduck-Léveillée *et al*., 2016) found that *hecA* was present in about 9% of the 100 fecal isolates from humans and animals, but *cj1349* was only found in 20% of the isolates.

Isolates linked to foods choices have also shown similar results. In their study on seafood isolates from India, (Martins *et al.*, 2023) discovered that 89% of the strains tested positive for *cadF* and 97.3% for cj1349, whereas only 11% tested positive for *hecA*. The core adhesion genes *cadF* and cj1349 were found in all *A. butzleri* isolates derived from milk, according to whole genome sequences by (Jazini *et al*., 2025). This suggests that these genes still play a role in host colonization regardless of where the bacteria was isolated from.

A study by Jazini *et al.*, indicated that the *HecA* with *PorA* genes may be one of the factors involved in strain-specific differences in colonization ability, while *CadF* and *Cj1349*, when combined, represent the primary adhesion mechanism of *A. butzleri* (Jazini *et al*., 2025). The abundance of these adhesives in many clinical, nutritional, and environmental isolates confirms their importance in host colonization and thus virulence factors (Figure 3).

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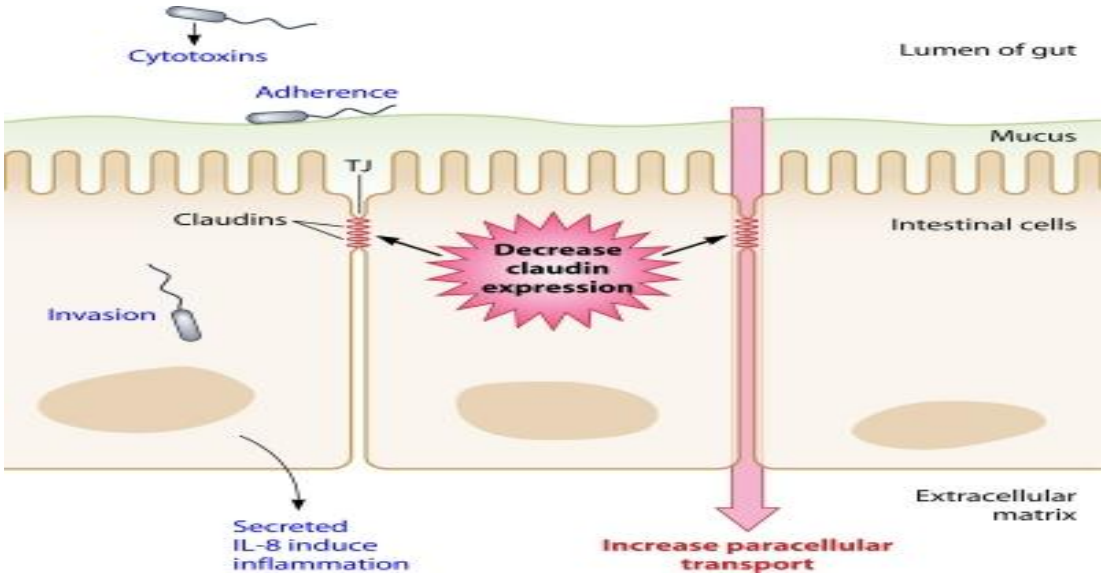

Figure 3: *A. butzleri* mechanisms of action on epithelial cells in this model: adherence, invasion, increased paracellular permeability, degradation of tight junction claudins and release of mediatory inflammation interleukin -8(Collado & Figueras, 2011).

➢ Iron Acquisition and Stress Adaptation

For successful infection, the host must be in an unfavorable environment, such as nutrient deficiencies and oxidative stress, which allows *A. butzleri* bacteria to thrive. Iron uptake and stress adaptation are associated with several genes, such as *irgA, iroE, fur*, the urease gene cluster (ureDABCEFG), *luxS*, and *htrA* (Fonseca *et al*., 2025).

Iron uptake is an essential process for the growth of pathogenic bacteria. This process is associated with *irgA* and *iroE*. For example, Fur regulates the iron homeostasis; luxS is used in quorum sensing and bacterial communication, etc. Similarly, *A. butzleri* genomes harbor a gene cluster that may help the bacterium survive in acidic environments like *Helicobacter pylori*. Another group of genes with a role in stress tolerance and host colonization is called *HtrA* (Buzzanca *et al.*, 2023). Overall, these adaptive mechanisms are likely to improve bacterial persistence within the host and complement the activity of the major virulence determinants, although their precise contribution to *A. butzleri* pathogenicity requires further investigation.

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Antimicrobial Resistance of *Arcobacter*

Antimicrobial resistance has become an increasing concern in *Arcobacter* spp., particularly because these bacteria have been recovered from diverse sources, including water, food, animals, and human clinical samples. Numerous studies have evaluated the antimicrobial susceptibility of *Arcobacter* isolates, with most investigations focusing on the clinically relevant species *A. butzleri*, *A. cryaerophilus*, and *A. skirrowii*, which are most frequently associated with human and animal infections (Ghaju Shrestha *et al.,* 2022). Methods such as agar dilution, broth micro-dilution, disc diffusion, gradient strip diffusion, and the Sensititre™ semi-automated system have been used to evaluate the sensitivity to antibiotics for Arcobacter isolates. The usual approach to treating infections caused by Arcobacter has included the use of quinolone, tetracycline, cephalosporin, macrolide, and combination of β-lactam and β-lactamase inhibitors.

More recently, Yusof *et al*. (2025) investigated agar dilution as a modal method of antimicrobial susceptibility testing for 415 *A. butzleri* isolates and provided tentative epidemiological cut-off (ECOFF) values for ciprofloxacin, erythromycin, gentamicin, and tetracycline.

There has been evidence of resistance against many kinds of antibiotics, even though these drugs are readily available. Various antibiotic classes have different reported resistance rates: penicillins (69.3% to 99.2%), cephalosporins (30.5% to 97.4%), macrolides (10.7 to 39.8%), fluoroquinolones (4.3 to 14.0%), aminoglycosides (1.8 to 12.9%), and tetracyclines (0.8 to 7.1%) (Ferreira *et al.*, 2019). Antimicrobial resistance determinants may be stored in *A. butzleri* since it consistently shows stronger resistance to many antimicrobial agents compared to other species in the genus (Ghaju Shrestha *et al*., 2022). Recent evidence, more information has been acquired about the multidrug-resistant (MDR) potential of *A. butzleri*. Chiarini *et al.* (2026) found that the *A. butzleri* strains isolated from poultry carcasses showed high resistance rates to tetracycline and ampicillin, in addition that bordetella genes involved in antimicrobial resistance and virulence-associated genes such as *tonB, hecB, mexA, mexB mviN, phoP tetR ylaC* were significantly overexpressed after exposure to selected disinfectants.

Constant contact with antimicrobial chemicals used in humans with veterinary medicine is probably the main cause of the rampant development of antibiotic resistance in *Arcobacter.* As a result, there is an increasing need for vigilant antibiotics management and ongoing monitoring of antimicrobial susceptibility due to the spread of resistant *Arcobacter* strains in water , foods, and the environment (Sciortino *et al*., 2021).

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Host Pathogen Interaction

Gastritis infection progression is an ever-changing process characterized by persistent interactions between the local gut microbiota, the host immune system, and the invading pathogen. To successfully colonize an intestinal environment, a pathogen must be able to bypass epithelial barriers, avoid host defensive mechanisms, and create a suitable niche(Gonzalez-Morales *et al.*, 2026). The severity of infection and the degree of inflammation determine the degree of the host response. Mammals are protected against intestinal infections by two additional defense systems: innate immunity (mediated by intestinal epithelial cells) and adaptive immunity(Medina *et al*., 2022). The first line of defense is known as innate immunity, which rapidly recognizes pathogens through specific pattern recognition receptors (PRRs), activates inflammatory signaling pathways, and stimulates the release of chemokines that facilitate the recruitment and activation of effector immune cells to sites of pathogen infection. B and T lymphocytes coordinate adaptive immunity to generate specific antigen-specific responses with immunological memory, providing long-lasting protection(Chen & Kolodkin-Gal, 2022). The intestinal mucosa contains a crucial epithelial barrier that protects the body from pathogenic bacteria and viruses. Epithelial cells interconnected by tight junction proteins, a protective mucus membrane, and a collection of antibacterial and immunomodulatory substances constitute this barrier.

The release of chemokines with cytokines as well as different signaling mediators helps coordinate immunological responses while also restricting bacterial invasion. In humans, *A. butzleri* and *A. cryaerophilus* have been associated with gastrointestinal disease (Martins *et al.*, 2022). In *C. jejuni*, host innate defenses have been suggested to contribute to the resolution of the infection, which occur several days of symptoms onset, as was also observed for *A. butzleri* and *A. skirrowii* human infections. Table 1, show recent studies on *A. butzleri*–host interaction.

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Table 1: Recent studies on *A. butzleri*–host interaction

Study	Study model / approach	Main findings	Recommended subsection
Baztarrika *et al*. (2025)	Human TLR reporter cells; pathogenic *Arcobacter* species including *A. butzleri*	*A. butzleri* hardly activated the TLRs, only TLR2/6 and TLR1/2, whereas *A. skirrowii* activated all tested TLRs.	Innate Immune Recognition and Complement Response
Chiarini *et al*. (2025)	C57BL/6J mice were orally infected with two strains *A. butzleri* strains; gut and faecal microbiota analysis	*A. butzleri* persisted in faecal samples up to day 4 and infection was associated with alterations in gut and faecal microbiota. The magnitude and pattern of microbiota changes differed according to the bacterial strain.	Host–Microbiota–Pathogen Interaction / end of Host Pathogen Interaction
Baztarrika *et al.* (2024) a	Caco-2 and HT29-MTX intestinal epithelial cells; single-gene knockout mutants	Inactivation of *cadF* caused a marked loss of adhesion, while *ciaB* and *flaAB* also contributed to adhesion and invasion. *cadF* was identified as a particularly important determinant.	Adhesion and Invasion
Baztarrika *et al.* (2024) b	65 food- and water-derived *Arcobacter* isolates; Caco-2 adhesion and invasion assays	*A. butzleri* displayed substantial adhesion and invasion capacity, with higher virulent activity than *A. cryaerophilus* in the Caco-2 model. Associations were investigated between pathogenic phenotype and *cadF*, *cj1349*, *ciaB*, and *hecA*.	Adhesion and Invasion
Baztarrika *et al.* (2023)	Two clinical *A. butzleri* isolates; whole-genome sequencing and Caco-2 infection assays	The clinical isolates carried determinants associated with flagellar function, chemotaxis, adhesion and invasion, but differed in their genetic profiles, including the presence of a urease cluster in one isolate.	Strain-dependent Pathogenicity / Host–Pathogen Interaction

Innate Immune Recognition and Complement Response

The innate immune response is the first line of defense against *Arcobacter butzleri* infection and is immediate, nonspecific, and generally effective during the initial 4–96 hours of infection. Pattern recognition receptors (PRRs) on innate immune cells such as macrophages, dendritic cells (DCs), and natural killer (NK) cells recognize pathogen-associated molecular patterns (PAMPs)/danger-associated molecular patterns (DAMPs) on invading pathogens. PRRs are a group of receptors such

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as Toll-like receptors (TLRs), C-type lectins, NOD-like receptors (NLRs), RIG-I-like receptors (RLRs), and AIM2-like receptors (ALRs). Upon activation, PRRs initiate classical signaling cascades to activate transcription factors (TFs), release proinflammatory cytokines such as TNF-α and IL-6, and induce inflammatory responses (Gonzalez-Morales *et al*., 2026). DCs play a key role as antigen-presenting cells and bridge the innate and adaptive immune systems. The adaptive immune response is a secondary immune response that develops hours to weeks after infection. It is highly specific for the antigen, effective but slow, and can develop immunological memory after the resolution of infection. The adaptive immune response is mediated by T and B lymphocytes, which recognize specific peptide antigens presented by MHC Class I and II molecules, respectively. Activation of T lymphocytes induces robust immunity involving cellular mechanisms mediated by CD8+ T cells and humoral mechanisms mediated by CD4+ T cells. Knowledge of the immune response against a specific pathogen is crucial for designing effective prophylactic vaccines and immunotherapeutics (Gölz *et al*., 2016).

In their study conducted by (Wilson *et al*., 2010) tested the bactericidal effect of normal human serum against *A. butzleri* isolates taken from various animals and environmental sources, such as chicken liver, pelican feces, bovine feces, shellfish, and water of river. They confirmed the crucial function of the complement cascades in suppressing *A. butzleri* infection by showing that most isolates were extremely vulnerable to complement mediated death and that bacterial survival increased significantly in complement-deficiencies serum.

Clinical reports of *A.butzleri* with *A.cryaerophilus* bacteremia suggest that some strains can avoid mediated complement clearance and spread outside the intestines, despite this overall serum susceptibility. Isolates from the circulation of *C. jejuni* are more resistant to complement than those from the intestinal bacteria, according to similar findings (Chiarini *et al*., 2024). According to these results, different Arcobacter strains may have different levels of serum resistance, which could explain why their pathogenic potential with clinical symptoms can vary.

A key host defense mechanism versus *A. butzleri*, according to the available evidence, is complementary mediated killing. Additional research is needed to understand the molecular

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mechanism of complement evasion, since some extremely dangerous isolates may be able to spread throughout the body due to strain dependent variations in serum resistance.

Cytokine Response and Inflammatory Mediators

After an infection with *A. butzleri*, the host quickly begins to activate its defense mechanisms, one of which is the generation of cytokines that promote inflammation. These intermediaries regulate the interaction among both adaptive and innate immunity, attract inflammatory cells, and increase antimicrobial activity to manage natural immunity. The cytokines profiles caused by *A. butzleri* has not been thoroughly studied, but what little is known suggests that infection initiates a strong inflammatory reaction including multiple important cytokines(Uljanovas *et al*., 2023).

The well-studied cytokine linked to Arcobacter infection is interleukin-8 (IL-8), although there are others. The interplay between human Caco-2 and porcine IPI-2I intestinal epithelial cells and four species of Arcobacter (*A. butzleri, A. cryaerophilus, A. skirrowii, and A. cibarius*) was examined by (Ho *et al*., 2007). Within two hours of infection, the study found that both cell lines significantly increased their IL-8 production, suggesting that stimulation of epithelial inflammatory signaling represents a common trait of the genus. Although bacterial adhesion and invasion were not associated with IL-8 production, this finding does not rule out the possibility that different strains of bacteria are subject to different regulatory mechanisms for cytokine induction (Buzzanca, 2022).

The response to inflammation caused by *A. butzleri* has been better understood because to new findings from murine infection models. Research by Ghaju Shrestha *et al.* found that various pro-inflammatory mediators, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-12p70 (IL-12p70) , interferon-gamma (IFN-γ), and monocytes chemoattractant proteins -1 (MCP-1) , were found to be substantially elevated in both the intestinal and systemic levels following experimental infection. The presence of these cytokines, along with increased nitric oxide generation and noticeable inflammatory cell infiltration, suggests that *A. butzleri* can trigger immunological activation on both the local and systemic levels. It is worth noting that different bacterial strains exhibited different levels of cytokine production, which indicates that the host's inflammatory reactions are strain specific (Ghaju Shrestha *et al*., 2022).

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According to scientific studies, interleukin-8 (IL-8) is a hallmark of early epithelial cell activation, while tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interferon-gamma (IFN-γ), monocyte chemoattractant protein-1 (MCP-1), and interleukin-12p70 (IL-12p70) all play a role in amplifying the cascade of inflammatory reactions upon invasion by *A. butzleri* (Lin *et al*., 2025; Matsushima *et al.*, 2022). However, our understanding of the cytokine network stimulated by this pathogen remains incomplete. Further research is needed to elucidate the mechanisms that regulate inflammation within the host organism and how these mechanisms relate to bacterial virulence and clinical outcomes.

Gölz *et al.* studied the immunopathological impacts of two invasive strains of *A. butzleri* in gnotobiotic IL-10-deficient mice. Despite persistent intestinal colonization, infected animals did not develop clinical symptoms, but the infection was associated with increased colonic epithelial apoptosis and immune cell infiltration including T and B lymphocytes, regulatory T cells (Tregs), macrophages and monocytes. This response was associated with increased TNF-α, IFN-γ, IL-6, IL-12p70, MCP-1 and nitric oxide together with signs of localised immune activation outside the intestine and systemic immune activation. These data demonstrate that *A. butzleri* is able to cause significant local and systemic inflammation in the absence of overt clinical disease, indicating crucial involvement for immune activation in its pathogenesis (Gölz *et al*., 2015).

Lactoferrin as a Biomarker of Intestinal Inflammation

Activated neutrophils are the primary secretors of lactoferrin, an iron binding glycoproteins, after inflammatory reactions. In addition to preventing bacterial development by storing iron, lactoferrin has antibacterial and immunomodulatory properties that aid in the body's natural defenses (Isidro *et al.*, 2020). It is well-known that fecal lactoferrin can be used as a biomarker to identify and track inflammatory responses in the intestines caused by invasive enteric infections (Chen *et al.*, 2011).

Patients in South Africa who had infections with *H.pylori*, Campylobacter species , and Arcobacter species. were studied by (Samie *et al*., 2007) for their fecal lactoferrin concentrations. While 34% from stool samples positive for *A .skirrowii* had elevated lactoferrin levels, 55% of *A. butzleri* samples had elevated levels. Lactoferrin concentrations in *A. butzleri*-positive patients were also lower than those in *Campylobacter jejuni* positive patients, but they were similar to those in *H. pylori*

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disease. *A. butzleri* is the most clinically significant pathogen within the genus Arcobacter, according to these findings, since it generates a higher intestinal inflammatory response than other species of Arcobacter (Samie *et al.*, 2007).

The immunopathogenesis for *A. butzleri*

Epithelial Barrier Disruption and Tissue Injury

Once *A. butzleri* has colonized the intestines, the body's innate immune system is its principal line of defense. Intestinal epithelial cells swiftly launch inflammatory signaling pathways during bacterial adhesion and invasion, enlisting immune cells to contain the invading bacteria. The immune-pathogenesis of *A.butzleri* has not been studied as thoroughly as *C. jejuni* or *H. pylori.* What little is known suggests that the main components of the initial host response include disruption of the epithelial barrier, activation of the complement system, and production of pro-inflammatory cytokines(Mahapatra, 2026).

Intestinal epithelial barrier disturbance is one of the most well-studied pathogenic processes. In study, Bücker looked at how *A. butzleri* interacted with human HT-29/B6 intestinal epithelial cells. They found that infection drastically lowered transepithelial electrical resistance, messed with tight junction architecture, and reduced claudin-1, claudin-5, and claudin-8 expression (Bücker *et al.*, 2009). Watery diarrhea, also known as leak-flux diarrhea, was caused by infected cells that showed signs of increased apoptosis and higher paracellular permeability. This research established a causal relationship between *A. butzleri* infection and epithelial damage and functioning of the intestinal barrier for the first time.

The innate immun0logical responses also includes the activation of inflammatory cytokines. All four species of Arcobacter that were investigated by Ho showed a considerable induction of IL-8 expression within the first hour of infection when they interacted with human (Caco-2) and swine (IPI-2I) intestinal epithelial cells(Nguyen, 2022). It is worth noting that there was no correlation between the amount of IL-8 production and bacterial adherence or invasion. This indicates that inflammatory activation could happen apart from bacterial internalization and that various strains of Arcobacter could use different pathogenic tactics. Instead of being seen as a direct indication of bacterial pathogenicity, this finding shows that IL-8 is more accurately seen as a measure of

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epithelial immune activation, demonstrating the intricacy of host pathogen interactions (Ferreira *et al.*, 2016).

Collectively, these studies suggest that the first line of defense against *A. butzleri* is to rupture the epithelial barrier, which in turn rapidly initiates the production of mediators of inflammation and sets in motion the complement cascade that kills the bacterium. Additional in vivo immunological studies are clearly required to understand the molecular mechanisms that control these responses and their role in disease severity (Chieffi *et al*., 2020).

Mechanisms of immune modulation by *A. butzleri*

Although evidence is growing that *A. butzleri* may trigger an illness, the molecular systems driving host immune control remain poorly understood. Recent evidence suggests that the bacteria actively affects numerous host cellular processes that dictate the course of disease, rather than only triggering an inflammatory response (Couto *et al.*, 2024).

Damage to the intestinal epithelial barrier occurs early in the pathogenic process. Researchers Martins found that when human HT-29/B6 intestinal epithelial cells were infected, they were drastically downregulated, leading to a significant rise in epithelial permeability and cell death. There is clear evidence that epithelial dysfunction is a key factor in the pathophysiology of *A. butzleri*, since these modifications led to leak-flux diarrhea and impaired barrier integrity (Martins *et al.*, 2022).

Differential cytokines responses also suggest inflammatory modulation. Experimental infection triggered broader pathways of inflammation including TNF-α, IL-6, IFN-γ, MCP-1, and IL-12p70, as shown by (Brückner *et al*., 2020), but (Ho *et al.*, 2007) indicated rapid activation of IL-8 in epithelial cells. The fact that these responses differed in intensity across different bacterial strains is intriguing since it suggests that immune activation is species-and strain-specific.

Research into *A. butzleri's* genome and transcription provides more evidence of its adaptive potential. During the early stages of infection, genes related to adhesion (*cadF*), invasion (*ciaB*), phospholipase activity (*pldA*), virulent (*mviN*), and motility (*flaA* & *motA*) were temporarily

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upregulated. The downregulation of these genes was demonstrated by (Medina et al., 2019) upon intracellular adaption. The biphasic transcriptional response of *A. butzleri* suggests that it may dynamically alter virulence gene expression in response to environmental stimuli, which could help it survive in unfavorable intracellular conditions (Buzzanca, 2022).

A. butzleri probably doesn't use just one immune evasion strategy to influence the immune system; instead, it does so through coordinating inflammatory signals, adaptive regulation of genes associated with virulence, and rupturing the epithelial barrier. The processes by which *A. butzleri* interacts with macrophages, adaptive immune responses, and dendritic cells remain unclear, nevertheless, and require additional research.

Conclusions

Acquiring a better understanding of *A. butzleri* as a pathogen that can be found in both water and food has significant implications for the health of humans as well as animals. Growing data suggests that a multitude of virulent factors promote its pathogenicity . These processes enable colonization of the intestines and set off the host's innate immune response, which includes activation of the complement system and the release of pro-inflammatory mediators, specifically IL-8, TNF-α, IL-6, and IFN-γ. However, *A. butzleri* pathogenesis is complex, and there is a lot of heterogeneity among strains when it comes to immune responses and virulence potential.

The molecular processes behind modulation of immunity as well as adaptive immune responses are among the numerous elements of host-pathogen interactions that have remained unclear, despite significant improvements in virulent profiling and comparative genomics. If we want to build better diagnostic tools, more precise antimicrobial treatments, and more efficient preventative measures, we need future studies that combine genomes, functional immunology, and in vivo infection models to confirm the functions of potential virulence factors. This overlooked enteric disease poses a significant threat to public health, hence it is critical that interdisciplinary studies focusing on a single health paradigm continue.

Conflict of interest

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The authors declare no conflict of interest.

Founding Source

No funding source

Authors contribution

The author was responsible for the experimental work, data analysis and preparation of the manuscript.

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