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Glycan-mediated adhesion mechanisms in antibiotic-resistant bacteria

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ABSTRACT

Bacterial adhesins play a central role in host-pathogen interactions, with many specifically targeting glycans to mediate bacterial colonization, influence infection dynamics, and evade host immune responses. In this review, we focus on bacterial pathogens identified by the World Health Organization as critical threats to public health and in urgent need of new treatments. We summarize glycoconjugate targets identified in the literature across 19 bacterial genera and species. This comprehensive review provides a foundation for the development of innovative therapeutic strategies to effectively combat these pathogens.

Introduction

The ESKAPE pathogens were initially identified as a group of multidrug-resistant bacteria that present an urgent need for effective therapies. This group, collectively known as the "ESKAPE bugs," includes *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* species [1]. With taxonomic revisions and the emergence of new threats, such as resistant *Escherichia coli* strains infections in immunocompromised individuals, there is growing recognition that the ESKAPE acronym may need to be updated to reflect these evolving challenges [2]. In addition to the ESKAPE pathogens, the 2024 World Health Organization (WHO) list highlights several other antibiotic-resistant bacteria that demand urgent attention. More pathogens were selected based on lethality, length of hospital stay, antibiotic resistance, ease of transmission, prevention options, available treatments, and whether new antibiotics are in development [3]. At the top of the priority list is multidrug-resistant and extensively drug-resistant *Mycobacterium tuberculosis*, reflecting its critical public health impact. The WHO also designates *Acinetobacter baumannii* and Enterobacteriales with carbapenem resistance and third-generation cephalosporin resistance as critical priorities for research and development. In the high-priority category, the list includes *Pseudomonas aeruginosa, Enterococcus faecium, Staphylococcus aureus, Shigella* species, *Salmonella* species (both Typhi and non-typhoidal), and *Neisseria gonorrhoeae*. The medium-priority group comprises Group A and Group B Streptococci, which exhibit resistance to macrolides and penicillin, respectively, along with *Streptococcus pneumoniae* and *Haemophilus influenzae*. These classifications highlight the urgent need for targeted efforts to develop new antibiotics and treatment strategies to address each of these resistant pathogens. Notably, *Helicobacter pylori* and *Campylobacter* species, which were included in the 2017 WHO list, are no longer part of the 2024 update. However, their relevance to antibiotic resistance remains significant and they will be included in this review.

Glycans are critical determinants that regulate the attachment of pathogens to the surface of host cells. In vertebrates, glycans are covalently linked to proteins and lipids, resulting in a diverse array of glycoproteins and glycolipids that are essential for host-bacterial interactions. Common monosaccharides involved in vertebrate glycosylation include mannose (Man), fucose (Fuc), glucose (Glc), galactose (Gal), *N*-acetylglucosamine (GlcNAc), glucosamine (GlcN), *N*-acetylgalactosamine (GalNAc) and sialic acid (Neu5Ac, Neu5Gc, Kdn for the most common). Mucins, which can be up to 80 % carbohydrate by molecular weight, are mostly O-glycosylated and are characterized by a core region, an elongated backbone, and a peripheral domain with various antigenic structures [4]. In addition, proteoglycans consist of a protein core linked to glycosaminoglycans (GAGs) and play an essential role in pathogen adhesion and invasion [5]. Extracellular matrix (ECM) glycoproteins such as fibronectin, laminin, and collagen are also highly glycosylated, maintaining tissue integrity and facilitating cellular interactions. In addition, glycolipids contribute to this complexity by serving as receptors for pathogens, facilitating their attachment to host cells, and modulating immune responses [6]. Bacterial adhesion to host

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List of acronyms

AIEC	Adherent Invasive *E. coli*
Ata	Trimeric Autotransporter Adhesin
BabA	Blood Group Antigen–Binding Adhesin
BFP	Bundle-Forming Pilus
CAZy	Carbohydrate-Active Enzymes Database
CbpA	Choline Binding Protein A
ClfA/ClfB	Clumping Factors A and B
CS	Surface Antigens
CUP	Chaperone-Usher Pathway
DAEC	Diffuse Adherent *E. coli*
DLL	"Dock, Lock, and Latch"
EAEC	Enteroaggregative *E. coli*
EcbA	E. faecium Collagen Binding Protein A
ECM	Extracellular Matrix
ECP	*E. coli* Common Pilus
EHEC	Enterohaemorrhagic *E. coli*
EIEC	Enteroinvasive *E. coli*
EPEC	Enteropathogenic *E. coli*
ESKAPE	*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter* spp.
ETEC	Enterotoxigenic *E. coli*
ExPEC	Extraintestinal Pathogenic *E. coli*
FHA	Filamentous Hemagglutinin
Fuc	Fucose
Gal	Galactose
GalCer	Galactosylceramide
GalNAc	*N*-acetylgalactosamine
GA1	Galβ1–3GalNAcβ1–4Galβ1–4Glc-ceramide
GA2	GalNAcβ1–4Galβ1–4Glc-ceramide
Gb3	Globotriaosylceramide
Gb4	Globoside
GBS	Group B *Streptococcus* / Guillain-Barré Syndrome (context-dependent)
GH	Glycosyl Hydrolases
Glc	Glucose
GlcN	Glucosamine
GlcNAc	*N*-acetylglucosamine
GP2	Glycoprotein 2
GAG	Glycosaminoglycan
GAS	Group A *Streptococcus*
HA	Hyaluronic Acid
HBHA	Heparin-Binding Hemagglutinin
HIF	*H. influenzae* Fimbriae
Hof	*Helicobacter* Outer Membrane
Hom	*Helicobacter* Outer Membrane
Hop	*Helicobacter* Outer Membrane Proteins
Hor	Hop-Related
Kdn	2-Keto-3-deoxy-D-glycero-d-galacto-nononic acid
KpSC	*Klebsiella pneumoniae* Species Complex
LabA	LacdiNAc-Binding Adhesin
LacNAc	N-acetyllactosamine
LPxTG	Leucine-Proline-X-Threonine/Serine/Alanine-Glycine Motif
LOS	Lipooligosaccharides
LPS	Lipopolysaccharide
Man	Mannose
Man3GlcNAc2	Oligomannose-3
Man5GlcNAc2	Oligomannose-5
Man6GlcNAc2	Oligomannose-6
MAM	Multivalent Adhesion Molecule
mAG	Mycolylarabinogalactan
MR/P	Man-Resistant *Proteus*-Like Fimbriae
MSCRAMM	Microbial Surface Components Recognizing Adhesive Matrix Molecules
MSHA	Mannose-Sensitive Hemagglutinin
MucBP	Mucin-Binding Protein
NAF	Non-Agglutinating Fimbria
Neu5Ac	*N*-acetylneuraminic Acid
Neu5Gc	*N*-glycolylneuraminic Acid
NHBA	Neisserial Heparin Binding Antigen
NhhA	*Neisseria* hsf Homologue
NTHi	Non-Typeable *Haemophilus influenzae*
nsSNPs	Nonsynonymous Single Nucleotide Polymorphisms
Omp	Outer Membrane Protein
OMPs	Outer Membrane Proteins
Opa	Opacity-Associated Protein
Pef	Plasmid-Encoded Fimbriae
PGC-3	Pilin Gene Cluster 3
Pls	Plasmin-Sensitive Protein
SabA	Sialic Acid-Binding Adhesin
Sdc1	Cell Surface Syndecan 1
sLea	Sialyl-Lewis^a
sLex	Sialyl-Lewis^x
SLN-Ac (2–3)	Neu5Acα2–3Galβ1–4GlcN
SLN-Ac (2–6)	Neu5Acα2–6Galβ1–4GlcNAc
SPR	Surface Plasmon Resonance
SRR	Serine-Rich Repeat
SRRP	Serine-Rich Repeat Glycoprotein
STEC	Shiga Toxin-Producing *E. coli*
T3SS	Type III Secretion System
T4bP	Type IVb Pilus
TAA	Trimeric Autotransporter Adhesin
TB	Tuberculosis
Uca	Urothelial Cell Adhesin
UPEC	Uropathogenic *E. coli*
UTI	Urinary Tract Infections
vWF	von Willebrand Factor
WHO	World Health Organization

cells, often mediated by lectins (carbohydrate-binding proteins that recognize specific sugar structures on host surfaces) is a critical step in the infection process, facilitating colonization and increasing resistance to immune responses and antibiotics. Targeting this initial adhesion with anti-adhesion therapies represents a promising strategy to prevent infection [7,8]. Therefore, insight into the role of glycosylation in bacterial adhesion may reveal new therapeutic targets and improve strategies to disrupt the early stages of infection. This review will focus on bacterial adhesins identified in the WHO's priority pathogen list, with emphasis on their interactions with host glycans. Adhesins include fibrillar structures (also called fimbriae or pili) [9], surface-exposed proteins, secreted proteins, and glycolipids (Fig. 1). We will review the currently described molecular mechanisms of these adhesin-glycan interactions, which may point to future developments of effective therapeutic interventions.

Critical priority list

Mycobacterium tuberculosis

Mycobacteria cause various diseases, including tuberculosis (TB), leprosy, and opportunistic infections. They interact with host immune

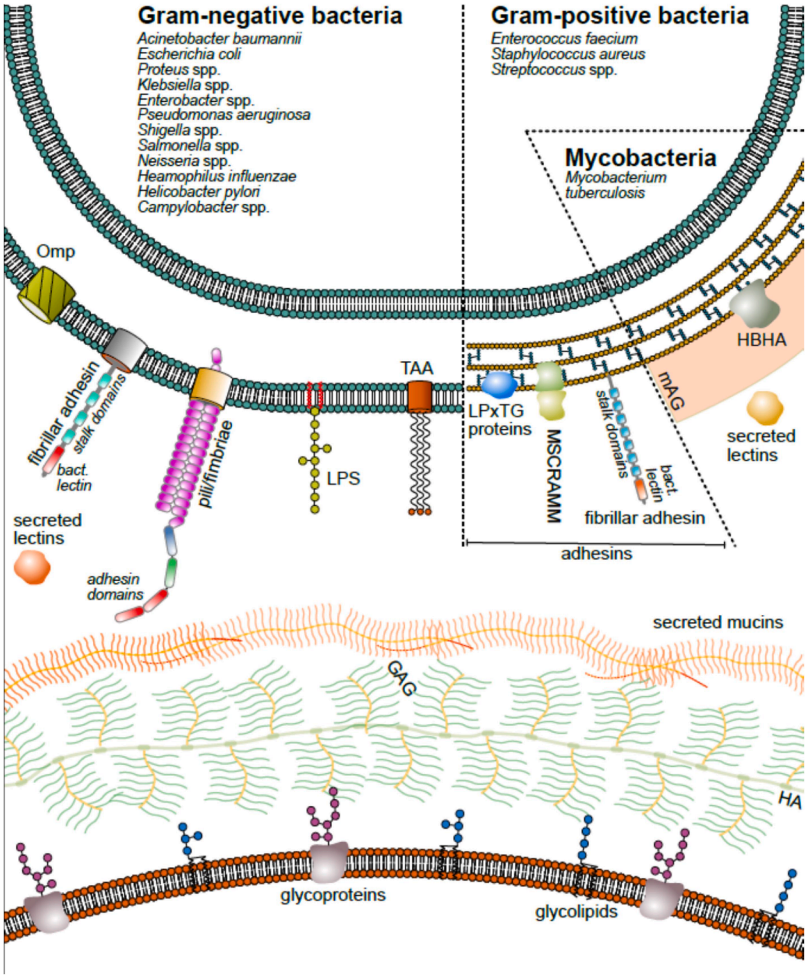

Fig. 1. Schematic representation of the main molecules involved in glycan-mediated adhesion phenomena between antibiotic-resistant bacteria and eukaryotic cells. The complementary abbreviations represent: Omp: outer membrane protein, LPS: lipopolysaccharide: TAA: trimeric autotranporter, LPxTG: enterococcal surface protein linked by a leucine-proline-X-threonine/serine/alanine-glycine motif, MSCRAMM: microbial surface components recognizing adhesive matrix molecules, mAG: mycolylarabinogalactan, HBHA: heparin-binding hemagglutinin, GAG: glycosaminoglycan, HA: hyaluronic acid.

cells, particularly macrophages, to proliferate and spread [10]. While numerous mycobacterial adhesins have been identified [11–16], limited information exists on lectin adhesins, their carbohydrate ligands, and functions [17–19] (Table 1). However, binding assays of *M. tuberculosis* (*M. tub*) on sugar-coated plates strongly suggested the presence of lectins on cell surfaces [19] and recent studies suggest mycobacterial lectins as potential drug targets and vaccine candidates for TB [20]. Genomic analyses have identified at least 94 potential lectins across mycobacteria, but only 11 in *M. tub* [17,18]. These include Ricin-type lectins, Man-specific C-type lectins, Man-sensitive hemagglutin, heparin-binding hemagglutinins, and filamentous hemagglutinin (FHA). Most of these remain structurally uncharacterized.

Table 1
This table lists glycans and monosaccharides recognized by mycobacterial species along with the corresponding literature.

Glycan/monosaccharide recognized	Literature
Yeast mannan	[31]
D-arabinose and mycobacterial arabinogalactan	[31]
Heparan sulfate proteoglycans, including Syndecan-4 (disaccharide repeat consisting of GlcNAc and glucuronic acid with sulfate on hydroxyl groups)	[21–23, 29]
Sulfated glycoconjugates	[24,39,40]
Galβ1–4GlcNAc in N-glycans	[34]
Sulfated Gal	[43,44]
GalNAc	[43,44]
Hyaluronic acid (disaccharide repeat consisting of GlcNAc and glucuronic acid)	[30]
Dermatan sulfate (disaccharide repeat consisting of GalNAc and iduronic acid with sulfate on hydroxyl groups)	[43,44]
Sialylated glycans	[43]

Mycobacterium tuberculosis lectin adhesins

Heparin-Binding Hemagglutinin (HBHA), a 22-kDa protein encoded by *rv0475*, is the most studied mycobacterial adhesin, essential for adherence to lung epithelial cells via heparan sulfate proteoglycans, which contain repeating disaccharide units of GlcNAc and glucuronic acid residues [21–23]. Its C-terminal lysine-rich domain binds sulfated glycoconjugates, promoting extrapulmonary dissemination [24]. Antibodies against HBHA reduce mycobacterial adhesion to epithelial cells. HBHA is present in multiple mycobacteria, including *M. leprae* and *M. marinum* [18]. It is also a proposed TB biomarker [25]. Additional functions include apoptosis induction in macrophages [26], actin reorganization [27], and lipid inclusion formation [28]. HBHA also interacts with syndecan-4 on alveolar epithelial cells [29]. Syndecans are a family of cell surface heparan sulfate proteoglycans. They are involved in cell adhesion, intercellular signaling, and tissue morphogenesis. The *M. tub* protein Rv3194c, primarily described as a protease, also binds hyaluronic acid (HA) found on pneumocytes [30]. The HA-binding site lies between amino acid residues 91–100 of Rv3194c. Overexpression of Rv3194c in *M. smegmatis* enhances persistent lung infections in mice

[30]. Another 12–14 kDa lectin named "mycotin" was isolated from *M. smegmatis* [31], and similar hemagglutinating proteins were identified in *M. tub* and *M. bovis* [32]. Their hemagglutination was inhibited by yeast polymannosylated N-glycoproteins (mannan), d-arabinose, and mycobacterial arabinogalactan [31], while mannan also blocked adhesion to macrophages [32]. Interestingly, d-arabinose was shown to disperse mycobacterial clumps [33]. The secreted *M. tub* protein sMTL-13, encoded by *rv1419*, is a ricin-type β-trefoil lectin [34]. It is found in *M. bovis* BCG, *M. marinum*, and *M. ulcerans*. sMTL-13 is detected in *M. tub* culture filtrates but not in non-tuberculous mycobacteria [34]. Patients with active TB show high levels of anti-sMTL-13 IgG and secrete IFN-γ [34]. sMTL-13 induces IL-6 production, contributing to TB resistance [35]. It was predicted as a drug target [36], and a DNA vaccine has shown strong immune responses in mice [37]. The protein modulates macrophage adhesion, and its recombinant form was crystallized [38], but the 3D structure remains unresolved. Its β-trefoil structure belongs to the ricin β family, which recognizes [Galβ1–4GlcNAc] patterns in host N-glycans. Additionally, four *M. tub* proteins (Rv0355, Rv1917, Rv3343, Rv3350) with sequence similarity to FHA, a 220 kDa protein in *Bordetella pertussis* that binds sulfated glycolipids and promotes biofilm formation were identified in *M. tub* [39,40]. While these proteins remain uncharacterized, molecular docking with fucoidan derivatives suggests potential applications for TB treatment [20].

Lectin adhesins in other mycobacterial species. Beyond *M. tub*, several potential lectins have been identified in other mycobacterial species. MUL_3720 from *M. ulcerans* is composed of a lectin domain initially recognized as binding Man and of a C-terminal LysM domain that binds peptidoglycan [41,42]. The first domain was later shown to bind sulfated Gal and GalNAc present in GAG like dermatan sulfate (disaccharide repeat consisting of GalNAc and iduronic acid) and keratin [43,44]. Orthologs have been identified in *M. marinum* (MMAR_3773) but are not documented in *M. tub* [42]. *M. ulcerans* cells interact with diverse glycans, including sialylated glycans, although in a MUL_3720-independent manner [43]. A sequence-database search for β-prism fold lectin domains identified MSMEG_3662, a 208-residue protein in *Mycobacterium smegmatis* [45]. This protein shares similarities with monocot Man-binding β-prism II fold lectins. Orthologs were identified in *M. abscessus* but not in *M. tub*. Based on crystallization and X-ray from *M. smegmatis* [45,46], the Man-binding domain was located in the N-terminal region, within the carbohydrate-binding module 50 (CBM50, also known as LysM domains) (http://www.cazy.org). In contrast, the C-terminal domain was shown to be responsible for binding to peptidoglycan. However, its role in host interaction remains unclear. *M. tub* Rv2075 shows sequence and secondary structure similarities with human Man receptor 2 and *C. elegans* proteins [17,18]. Orthologs of Rv2075c have been identified in multiple *M. tub* strains [18]. This lectin is predicted to be located in the outer membrane [47]. *rv2813* and *rv3659* genes encode Man-sensitive hemagglutinin (MSHA)-like proteins, with Rv2813 sharing similarities with *Vibrio cholerae* MSHA D, essential for erythrocyte agglutination [48]. Recent studies have also shown that *M. ulcerans* exhibits high affinity for sulfated glycans and keratin [43,44]. Furthermore, the discovery of mycobacterial pili [49–51] opens new avenues to explore lectins within these structures.

Acinetobacter baumannii

A. baumannii is an emerging opportunistic pathogen responsible for infections in multiple body sites, including the lungs, bloodstream, skin, urinary tract, and soft tissues [52]. Despite its clinical significance, limited data are available on *A. baumannii* adhesins (Table 2). Among its characterized virulence factors is the trimeric autotransporter adhesin (Ata), which plays a critical role in the bacterium's ability to adhere to host cells and tissues. This adhesin has been shown to interact with components of the extracellular matrix of the host cell via specific glycans, including Gal, GlcNAc, and Gal(β1–3/4)-GlcNAc [53]. Furthermore, the adhesion onto respiratory tract epithelial cells of CsuA/BABCDE pilus of *A. baumannii*, another adhesin, is inhibited by Man [54]. Adding to these adhesins, the *A. baumannii* pili Abp1 and Abp2 are part of the chaperone-usher pathway (CUP) and are equipped with the adhesins Abp1D and Abp2D, which specifically bind to biantennary N-glycans. This biantennary glycan consists of two GlcNAc residues attached to a central trimannose moiety, with each branch containing a terminal GlcNAc and Gal [55]. In addition, *A. baumannii* possesses yet unidentified adhesins on its surface that can bind to various glycosphingolipids, including lactotetraosylceramide (Lc4Cer) (Galβ1–3GlcNAcβ1–3Galβ1–4Glc-ceramide) and neolactotetraosylcer amide (nLc4Cer) (Galβ1–4GlcNAcβ1–3Galβ1–4Glc-ceramide) via GlcNAc [56]. Conversely, the AbFhaB/FhaC two-partner secretion system has been identified to bind extracellular matrix glycoproteins such as fibronectin, although details of the glycan component of this interaction remain unknown [57].

Table 2
This table lists glycans and monosaccharides recognized by *Acinetobacter baumannii* and the corresponding literature.

Glycan/monosaccharide recognized	Literature
Gal(β1–3/4)-GlcNAc	[53]
D-man	[54]
Biantennary N-glycans with a trimannose backbone	[55]
Lc4Cer	[56]
nLc4Cer	[56]

Enterobacterales

E. coli

Typically, *E. coli* is a commensal bacterium in the gastrointestinal tract of vertebrates, but certain strains express virulence factors allowing them to become pathogenic in humans and animals. These pathogenic strains cause a range of infections, from intestinal diseases such as diarrhea to extraintestinal infections such as urinary tract infections, sepsis, and meningitis. The major pathotypes include enterotoxigenic *E. coli* (ETEC), enteropathogenic *E. coli* (EPEC), enterohaemorrhagic *E. coli* (EHEC) including the shiga toxin-producing *E. coli* (STEC), enteroaggregative *E. coli* (EAEC), diffuse adherent *E. coli* (DAEC), enteroinvasive *E. coli* (EIEC), adherent invasive *E. coli* (AIEC), and extraintestinal pathogenic *E. coli* (ExPEC), which includes uropathogenic (UPEC), meningitic, and bloodborne strains [58].

Numerous pili, commonly known as fimbriae, have been extensively studied for their molecular recognition properties in *E. coli* (Table 3). These structures typically possess a lectin domain at the tip of their filamentous appendages. The type 1 pilus, in particular, has received considerable attention due to the presence of the FimH protein at its tip, which is critical for the virulence UPEC, the major cause of urinary tract infections (UTI) [59]. In addition, type 1 pilus of both *Salmonella* and *E. coli* have been shown to facilitate pathogenesis by mediating adhesion to and promoting internalization on a variety of host cells, including epithelial, endothelial, and lymphoid cells [60]. FimH contains a lectin domain that exhibits a specific binding affinity for Man. Its primary natural receptor is the uroplakin glycoprotein, which is highly expressed on the epithelial cells of the urinary tract [61–64]. In addition, glycoprotein 2 (GP2), which is specifically expressed on the apical plasma membrane of M cells within the intestinal epithelium, is also recognized by the type 1 pilus and functions as a transcytotic receptor for mucosal antigens [65]. FimH targets oligomannosylated N-glycans, with oligomannose-3 ($Man_3GlcNAc_2$) and oligomannose-5 ($Man_5GlcNAc_2$) showing the strongest binding through their Manα1,3Man branch. The addition of an α1–2 linked Man to form oligomannose-6 ($Man_6GlcNAc_2$) shields this high-affinity site, facilitating cooperative bivalent binding of multiple FimH molecules, which further enhances the interaction [66].

Table 3
This table lists glycans and monosaccharides recognized by *Escherichia coli* and the corresponding literature.

Glycan/monosaccharide recognized	Literature
Man	[59,60,65–67]
Gb3	[58,68,69]
Gb4	[68,69]
LacNAc	[70,71,73,74,91–93]
GalCer	[72–74]
GA2	[72–74]
GA1	[72–74]
Sialic acid	[75–77,86,87]
GlcNAc	[78]
Lactotriaosylceramide	[80]
Lactotetraosylceramide	[80]
Blood group H and B	[83]
Sialyl-lacto-*N*-fucopentose VI	[84]
Sulfatide	[81,82,85]
β-GalNAc-1,4β-Gal	[74,88]
Glucosylceramide	[90]
Lactosylceramide	[73,74,90]
Le^a, Le^x, Le^y	[90]
Neolactotetraosylceramide	[90]
Gangliotriaosylceramide	[90]
Gangliotetraosylceramide	[90]
3-*O*-sulfated galactose	[96]
GalNAc	[98,99]

In combination with this specificity, FimH uses catch bonds to enhance its binding capacity. Catch bonds are specialized receptor-ligand interactions that strengthen under mechanical force and have longer lifetimes, in contrast to typical slip bonds that weaken under increasing tension. FimH undergoes a force-induced conformational shift from an open to a closed state, increasing the stability of the binding. The closed binding pocket in FimH restricts ligand escape, making it highly resistant to dissociation under force and contributing to the longevity of the binding [67].

During ascending UTIs, UPEC utilize P-pili to attach to glycolipid receptors on the surface of renal epithelial cells, with the adhesin PapG, located at the tip of the P-pilus, playing a crucial role in this binding. The receptor for PapG is globotriaosylceramide (Gb3), which consists of a digalactoside core (Galα1–4 Gal) linked by a β-Glc residue to a ceramide group; variations in this receptor family, such as the addition of GalNAc to form Gb4 (globoside), can also be recognized by PapG. This interaction is essential for bacterial colonization of the kidneys and is a key factor in developing pyelonephritis, a severe kidney infection [68,69].

The adhesin FmlH, located at the tip of the F9 pilus facilitates adhesion to terminal Gal linked in β1–3 to GlcNAc, forming the Galβ1–3GlcNAc sequence, also known as type 1 GalNAc. This terminal LacNAc type 1 is present in core-1 and −2 O-glycans of inflamed urothelium and is linked to the persistence of UPEC during chronic cystitis in an acute mouse model [70,71].

ETEC strains isolated from pigs with post-weaning diarrhea produce different pili than ETEC strains that infect humans, including pili K88 and F18. In addition, ETEC strains causing neonatal diarrhea in piglets are typically associated with pili K99, F6 (also known as porcine antigen 987), and F41 (without known glycoreceptors so far), which show little correlation with post-weaning diarrhea [72]. The K88 pilus also known as F4 binds to GalCer (Gal-ceramide) with hydroxylated fatty acids, GA2 (GalNAcβ1–4Galβ1–4Glc-ceramide), GA1 (Galβ1–3GalNAcβ1–4Galβ1–4Glc-ceramide), and lactosylceramide (Galβ1–4Glc-ceramide) via galactosyl residues in glycosphingolipids [73,74]. K99 pilus, also called F5, was shown to bind to sialic acid [75] from gangliosides [76] and porcin mucins [77]. F17 G fimbriae promote binding to GlcNAc-containing receptors on the microvilli of the intestinal epithelium of ruminants [78]. Five F17 G variants exhibit different binding specificities, with F17aG having the highest affinity for $HOOC(CH_3)CH_3$–3-*O*-GlcNAcβ1–4GlcNAcβ, mainly due to its higher positive charge from additional lysines and arginines compared to F17bG. While F17aG also binds well to doubly sulfated Galβ1–4GlcNAc, F17bG affinity for this sugar is significantly lower, possibly due to the mutation of Asn90 to Lys90 in F17aG, which affects the interactions with sulfate ion. In addition, F17bG binds disialylated lactose [79].

F6 binds to the glycosphingolipids lactotriaosylceramide (GlcNAcβ1–3Galβ1–4Glc-ceramide) and lactotetraosylceramide (Galβ1–3GlcNAcβ1–3Galβ1–4Glc-ceramide) via a neolacto core chain (Galβ1–4GlcNAc) [80]. A class of pili related to F6, termed colonization factors or coli surface antigens (CS), has been identified in human-associated ETEC. They include CS12, CS18, CS20, and CS30. CS30 is found in ETEC isolates from children with diarrhea worldwide, underscoring their clinical significance. The operon structure of CS30 is highly conserved and closely resembles the operon architecture of F6, suggesting a common evolutionary origin and functional similarities across host species. The major subunit of CS30, CsmA, shares over 50 % amino acid identity with the major subunit of F6, FasA. In addition, the CS30-binding glycosphingolipid from human small intestine was identified as sulfatide (SO_3–3Gal-ceramide) [81,82].

F18 pili encoded by the *fed* gene cluster found in ETEC and STEC are known to bind via the adhesin FedF to glycosphingolipids having blood group H type 1 determinant (Fucα1–2Galβ1–3GlcNAcβ1–3Galβ1–4Glc). Notably, the affinity increases when a terminal α3-linked Gal or GalNAc is added, forming the blood group B (Galα1–3(Fucα1–2)Galβ1–3GlcNAcβ1–3Galβ1–4Glc) or A (GalNAcα1–3(Fucα1–2)Galβ1–3GlcNAcβ1–3Galβ1–4Glc) determinants respectively on small intestinal epithelium [83].

Ucl pilus (also previously annotated as F17-like or Uca-like pilus) are key attachment factors that promote adherence of ExPEC. Among 358 glycans tested, Ucl pili were found to bind to four specific glycans, three of which were sialylated and three α1–3 fucosylated. The highest binding affinity was observed for sialyllacto-*N*-fucopentose VI, highlighting its role as a critical receptor for these pili (Neu5Acα2–6Galβ1–4GlcNAcβ1–3Galβ1–4(Fucα1–3)Glc) [84].

CS6 pili from ETEC bind specifically to sulfatide (SO_3–3Gal-ceramide) on glycosphingolipids. This binding is mediated by the CssB subunit of the CS6 complex and is inhibited by dextran sulfate. Sulfatides are found located in the human or rabbit small intestine [85].

S-type fimbriae (Sfa) from ExPEC bind specifically to NeuAcα2–3-Gal on glycolipids and glycoproteins through the SfaS adhesin [86,87]. Similarly, F1C pili from UPEC can adhere to βGalNAc1–4βGal found on asialo-GM2 and asialoGM1 present in epithelial cells [74,88]. Like P and S pili, F1C pili have evolved to withstand the specific conditions of the upper urinary tract [89].

Colonization factor antigen (CFA/I) from ETEC is a pilus without distinct tip structure binding to many different glycosphingolipids: glucosylceramide (Glc-ceramide), lactosylceramide (Galα3Galβ4Glc-ceramide and Galα3Galα3Galβ4Glc-ceramide) with $lewis^a$ epitope (Galβ1–3(Fucα1–4)GlcNAcβ1–3Galβ1–4Glc-ceramide), neolactotetraosylceramide (Galβ1–4GlcNAcβ1–3Galβ1–4Glc-ceramide, Galα1–3Galβ1–4GlcNAcβ1–3Galβ1–4Glc-ceramide) with blood group H (Fucα1–2Galβ1–4GlcNAcβ1–3Galβ1–4Glc-ceramide), $lewis^x$ (Galβ4(Fucα3)GlcNAcβ3Galβ4Glc-ceramide) and $lewis^y$ (Fucα1–2Galβ1–4(Fucα1–3)GlcNAcβ1–3Galβ1–4Glc-ceramide), gangliotriaosylceramide (GalNAcβ1–4Galβ1–4Glc-ceramide) and gangliotetraosylceramide (Galβ1–3GalNAcβ1–4Galβ1–4Glc-ceramide) [90].

The bundle-forming pilus (BFP), also known as the type IVb pilus (T4bP) of EPEC, is essential for initial host cell attachment. Its major structural component acts as a lectin, allowing EPEC to bind specifically to *N*-acetyllactosamine (LacNAc) glycan receptors on host cell surfaces. Incubation of EPEC with synthetic LacNAc-bearing neoglycoconjugates not only blocks this adhesion, but also promotes BFP retraction, leading to subsequent degradation of T4bP subunits [91–93].

Of the 58 pili identified in *E. coli*, the molecular receptors for many of these adhesins remain to be elucidated. However, a significant number of studies have shown that the intestinal mucosa serves as a receptor for several types of pili [94]. Furthermore, EPEC and EHEC O157 adherence to HT-29 cells decreases with cell differentiation and following

disruption of O-glycan biosynthesis. The absence of core 2 O-glycans further reduces the adhesion of these pathogens, highlighting the need to identify additional adhesins involved in this process [95]. Other than pili, the multivalent adhesion molecule (MAM) of the intestinal commensal *E. coli* recognize a common 3-*O*-sulfogalactosyl moiety found in mucin. Desulfation of mucin reduced bacterial binding and increased attachment to epithelial surfaces through interactions with sulfated lipids and proteins [96].

EtpA, an exoprotein adhesin secreted via the two-partner system in ETEC, binds to the conserved region of flagellin by attaching to the uncapped tips of the flagellum. This interaction forms a "bridge" that facilitates the indirect adhesion of flagella to intestinal mucosal tissues [97]. Once at the host epithelium, EtpA binds directly to GalNAc as the terminal monosaccharide of the human A blood group on enterocyte surfaces and secreted mucins such as MUC2 [98]. People with blood group A thus appear to be more likely to develop moderate to severe diarrhea when infected with the EtpA-producing ETEC [99].

Proteus spp

The genus *Proteus* is classified in the newly established family Morganellaceae, part of the order Enterobacteriales [100]. *Proteus* comprises six species, including *P. mirabilis, P. vulgaris*, and *P. penneri*, which are typically considered opportunistic pathogens with relatively low virulence. Among these, *P. mirabilis* can cause a variety of human infections involving wounds, the eyes, the gastrointestinal tract, and the urinary tract [101]. Sequencing of the clinical isolate *P. mirabilis* HI4320 allowed to predict 17 chaperone fimbrial operons, with a high degree of conservation in the major structural subunit proteins for 14 of these pili among 58 clinical isolates [102]. However, to date, only a small number of pili encoded by *P. mirabilis* (Table 4) have been characterized among which Man-resistant *Proteus*-like (MR/P) and urothelial cell adhesin (Uca) (or non-agglutinating fimbria, NAF). The MR/P pilus features MrpH as its tip-located adhesin, which may interact with acidic protein side chains or sialoglycans. It contains a transition metal center, where Zn^{2+} is coordinated by three conserved histidine residues, alongside a ligand-binding site [84,103]. While the tip-adhesin from Uca, UcaD binds to TF antigen-β1–3 Gal (Galβ1–3GalNAcβ1–3 Gal), 6-*O*-sulfated-sialyl-lewis^x (Neu5Acα2–3(6-*O*-Sul)Galβ1–4(Fucα1–3)GlcNAcβ), biantennary lactosamine-Tn-antigens (Galβ1–4GlcNAcβ1–6 (Galβ1–4GlcNAcβ1–3)GalNAcα) and GT3 glycan moiety (Neu5Acα2–8Neu5Acα2–8Neu5Acα2–3Galβ1–4Glc) with high affinity [84]. Uca pili are phylogenetically related to Ucl pilus from *E. coli* and F17/G pilus from ETEC. However, none of the key residues observed in the F17/G or Ucl binding pockets are conserved in the tip-adhesin UcaD, suggesting differences in ligand recognition despite their evolutionary relationship [104].

Klebsiella spp

Klebsiella spp. are opportunistic pathogens that can cause a variety of infections, including pneumonia, soft tissue and surgical site infections, urinary tract infections, bloodstream infections, and sepsis. The genus includes a wide range of species, most notably the *Klebsiella pneumoniae* species complex (KpSC) and several more genetically distinct species such as *K. indica, K. terrigena, K. spallanzanii, K. huaxiensis, K. oxytoca, K. grimontii, K. pasteurii*, and *K. michiganensis*. The KpSC, includes species that are closely related to *K. pneumoniae sensu stricto* and share an average nucleotide identity of 95–96 %. Seven KpSC phylogroups were identified, including *K. pneumoniae* (Kp1), *K. quasipneumoniae* subsp. *quasipneumoniae* (Kp2), *K. variicola* subsp. *variicola* (Kp3), *K. quasipneumoniae* subsp. *similipneumoniae* (Kp4), *K. variicola* subsp. *tropica* (Kp5), *K. quasivariicola* (Kp6), and *K. africana* (Kp7) [105].

Similar to UPEC, *K. pneumoniae* relies on FimH-tipped type 1 pili to adhere to and invade bladder epithelial cells. *K. pneumoniae* FimH is predominantly in a low-affinity state. However, isolates from patients with long-term indwelling catheters were shown to possess relaxed, high-affinity FimH variants. These variants enhance *K. pneumoniae* fitness in bladder infection models, suggesting that prolonged residence in the urinary tract may be selected for these higher-binding FimH variants [106]. Type 3 pili are found primarily in *Klebsiella* spp. (detected in 95 % of *K. pneumoniae* isolates), as well as in *Enterobacter, Serratia, Proteus, Providencia*, and *Citrobacter* species. However, they occur in only about 2 % of *E. coli* isolates. These fimbriae belong to the chaperone/usher family encoded by the mrkABCDF gene cluster, where mrkA encodes the major structural subunit and mrkD encodes the fimbrial adhesin [107]. MrkD binds to collagen types IV and V [108]. Type 1 pili mediate Man dependent agglutination of yeast, whereas type 3 pili mediate Man-resistant agglutination [109]. Although the exact structure of the glycan target remains unclear, type 3 pili contain two domains similar to those of type 1 pili that allow catch-bond-like binding [107]. *K. aerogenes* uses the CUP1-mediated chaperone-usher (CU) pili system to bind and colonize the inflamed intestinal mucosa, but not the oral mucosa, although the exact molecular target is not known [110] (Table 5).

Enterobacter spp.

The genus *Enterobacter* currently contains 22 identified species, of which *E. aerogenes, E. cloacae*, and *E. hormaechei* are the most isolated in clinical infections. These species are often associated with infections in immunocompromised patients and those in intensive care units. *Enterobacter* spp. have been implicated in a variety of infections, including cerebral abscess, pneumonia, meningitis, septicemia, and infections of the urinary tract (especially catheter-associated), wounds, and abdominal or intestinal tract [111]. In *E. hormaechei* subsp. *hoffmannii*, the mrkABCDF locus encoding type 3 pilus is commonly found on plasmids. Although type 3 fimbriae are not widely distributed across the species, they may confer a fitness advantage to certain *E. hormaechei* strains A 35 kDa pilus subunit in *E. cloacae*, showing over 85 % identity to FimH in *S.* Typhimurium, functions as a lectin that specifically recognizes and binds to high-mannose structures, particularly $Man_9GlcNAc_2$ [112]. Notably, around 50 % of *Enterobacter* spp. isolates from a hospital in Egypt were found to carry the *fimH* gene [113]. Despite these findings, the literature on adhesins in Enterobacter spp. remains scarce. (Table 6).

Other Enterobacteriales

Other Enterobacteriales, such as *Serratia* spp., *Citrobacter* spp., *Morganella* spp., *Raoultella* spp., *Providencia* spp., *Pantoea* spp., *Yersinia* spp., *Cronobacter* spp., *Kluyvera* spp., *Budvicia* spp., *Buttiauxella* spp., *Edwardsiella* spp., *Hafnia* spp., and *Cedecea* spp., are increasingly concerning due to their ability to develop antibiotic resistance [114]. They represent a critical area for future research, as many of them are still poorly characterized in terms of their ability to bind glycoproteins.

Table 4
This table lists glycans and monosaccharides recognized by *Proteus* spp. and the corresponding literature.

Glycan/monosaccharide recognized	Literature
Sialoglycans, GT3	[84,103]
TF antigen-β1–3Gal	[84]
6-*O*-sulfated-sialyl-Lewis^x	[84]
Biantennary lactosamine-Tn-antigens	[84]

Table 5
This table lists glycans and monosaccharides recognized by *Klebsiella* spp. and the corresponding literature.

Glycan/monosaccharide recognized	Literature
Mannose-containing glycans	[109]
Unknown glycan target in the inflamed intestinal mucosa	[110]

Table 6
This table lists glycans and monosaccharides recognized by *Enterobacter cloacae* and the corresponding literature.

Glycan/monosaccharide recognized	Literature
$Man_9GlcNAc_2$	[112]

High priority list

Pseudomonas aeruginosa

P. aeruginosa is associated with increasing infections, primarily in healthcare settings. These infections are prevalent in immunocompromised individuals, including burn victims, patients with cystic fibrosis, acute leukemia, organ transplant recipients, and intravenous drug users [115]. The interaction between *P. aeruginosa* and glycans has been characterized for many types of glycans among which N-glycans have been identified as ligands for adhesion to epithelial cells and macrophages [116,117]. *P. aeruginosa* can also bind complex glycans in glycolipids [118], GAGs [116], chitin (disaccharide on GlcNAc linked in β1–4) [119], and mucin glycans [120]. Interestingly, the latter have also been described to attenuate *P. aeruginosa* virulence by downregulating the type VI secretion system [121,122] (Table 7).

P. aeruginosa flagellum plays a crucial role in pulmonary infection by binding to specific glycolipids containing α2,3-linked Neu5Ac residues on lung epithelial cells. It binds to the terminal sialic acid of GM1 (NeuAcα2–3Galβ1–3GalNAcβ1–4(Galβ1–4Glc-ceramide)) and GD1a (NeuAc-α2–3Galβ1–3GalNAcβ1–4(Galβ1–4Glc-ceramide)) on the apical surface. It also binds asialo-GM1 (Galβ1–3GalNAcβ1–4(Galβ1–4Glc-ceramide)) but with a lower affinity [123–125]. Additionally, flagella interact with heparan sulfate proteoglycans on the basolateral surface and to $Lewis^x$ and sialyl-le^x through the cap of the Flagella; FliD on the strain PAO1. The Type IV pilus (T4P) further facilitates infection by binding to N-glycans on the apical surface of polarized lung epithelial cells [126,127]. The same pilus has been identified to recognize GalNAcβ1–4 Gal disaccharide, present in asialo-GM1 and asialo-GM2 (GalNAcβ1–4(Galβ1–4Glc-ceramide)) [128].

Whole bacterial cells have been reported to bind to type 1 (Galβ1–3GlcNAc) and type 2 (Galβ1–4GlcNAc) glycan epitopes as well as to GalNAcβ1–4 Gal; however, the specific adhesins responsible for this recognition have not been investigated [129,130].

Table 7
This table lists glycans and monosaccharides recognized by *Pseudomonas aeruginosa* and the corresponding literature.

Glycan/monosaccharide recognized	Literature
N-glycans	[116, 117]
Complex glycans in glycolipids	[118]
Glycosaminoglycans	[116]
Chitin (disaccharide on GlcNAc linked in β1–4)	[119]
Mucin glycans	[121, 122]
GM1	[123, 125]
GD1a	[123, 125]
Heparan sulfate (disaccharide repeat consisting of GlcNAc and glucuronic acid with sulfate on hydroxyl groups)	[128]
Le^x and sialyl-le^x	[126, 127]
GalNAcβ1–4 Gal (present in asialo-GM1 and asialo GM2)	[128]
Type 1: Galβ1–3GlcNAc and Type 2: Galβ1–4GlcNAc	[129, 130]
Fuc	[131]
Gal	[131]
Gb3, iGb3	[132, 133]

P. aeruginosa produces two cytoplasmic lectins, LecA (PA-IL) and LecB (PA-IIL), which bind specifically to d-Gal and l-Fuc, respectively [131]. During infection, bacterial cell lysis releases tetrameric LecA, which bridges the bacterial envelope to Gal disaccharides present on tissue glycolipids, including globotriaosylceramide (Gb3, Galα1–4Galβ1–4Glc) and isoglobotriaosylceramide (iGb3, Galα1–3Galβ1–4Glc) [132]. This interaction triggers membrane engulfment of the bacterium through a "lipid zipper" mechanism, facilitating its internalization into host cells [133].

Enterococcus faecium

Enterococcus faecium is a commensal organism in the intestinal microbiota of humans and animals that has evolved over the past four decades into a feared multidrug-resistant nosocomial pathogen responsible for infectious endocarditis, urinary tract infections, intra-abdominal infections, meningitis, surgical site infections, and septicemia [134]. *E. faecium* expresses several adhesins that interact with host glycoproteins, particularly components of the ECM, although the specific role of glycans in these interactions remains unclear.

E. faecium and other Gram-positive cocci, like *Staphylococcus aureus* produces a variety of surface proteins that are covalently linked to the cell wall peptidoglycan through a leucine-proline-X-threonine/serine/alanine-glycine (LPxTG) motif and play a critical role in host colonization and infection progression. These cell wall-anchored proteins are typically categorized according to their structural and functional properties. Among the most common types are microbial surface component-recognizing adhesive matrix molecules, a family of proteins characterized by the presence of two adjacent IgG-like folded subdomains that are involved in ligand binding [135]. In *E. faecium,* 15 predicted microbial surface components recognizing adhesive matrix molecules (MSCRAMM) proteins were identified predominantly in clinically derived isolates [136].

Among them, Acm (adhesin of collagen from *E. faecium*) that interacts with collagen type I and to a lesser extent with collagen type IV [137,138], Scm (for second collagen adhesin of *E. faecium*) binds to collagen type V and fibrinogen like EcbA (for *E. faecium* collagen binding protein A) [139]. However, due to the limited repertoire of surface proteins, individual bacterial proteins have undergone selective pressure to evolve multifunctionality, allowing them to play different roles in colonizing host tissues by having multiple ligands and evading the immune system [135].

Interestingly, the comparison of pilin gene cluster 3 (PGC-3) of *E. faecium* E1165 and the SpaCBA pili of *Lacticaseibacillus rhamnosus* GG, a human gut-adapted and health-benefiting probiotic strain, revealed a high level of sequence similarity between the two pilus gene clusters. Pilus-mediated interaction between *E. faecium* and host mucus could be inhibited by targeting these structures through competitive binding of the L. *rhamnosus* GG SpaC protein [140]. The SpaC protein can recognize Man and may bind to longer intestinal mucin oligosaccharides. It also appears capable of forming a Fuc binding site similar to that found in F-type lectins, although it lacks the typical structural features of C-type lectins. This suggests that SpaC may represent an unconventional lectin with diverse glycan recognition capabilities [141]. The functional similarity between SpaC and PGC-3 to mucus-binding pili raises the possibility that PGC-3 binds to mucins via glycans, similar to SpaA. Examples from other bacterial species highlight the versatility of MSCRAMMs. For instance, the N-terminal domain of RadA from *Ruminococcus gnavus* not only binds collagen, like many MSCRAMMs, but also recognizes human immunoglobulins (IgG and IgA) and glycans present on intestinal mucins. This glycan interaction can be competitively inhibited by monosaccharides such as Gal and GalNAc [142] (Table 8).

Staphylococcus aureus

Staphylococcus aureus is a common bacterial pathogen responsible for

Table 8
This table lists glycans and monosaccharides recognized by *Enterococcus faecium* and the corresponding literature.

Glycan/monosaccharide recognized	Literature
Man	[140]
Fuc	[141]

many uncomplicated skin infections and a variety of serious invasive infections worldwide each year. It is a major cause of pneumonia and other respiratory tract infections, surgical site, prosthetic joint and cardiovascular infections, and is a leading cause of hospital-acquired bacteremia [143]. Like *E. faecium, S. aureus* expresses a diverse array of MSCRAMMs that facilitate adhesion to various ECM components and support biofilm formation. As a typical sortase anchored protein, these proteins are attached to the cell wall via a C-terminal LPxTG motif [135]. The fibronectin-binding proteins, FnBPA and FnBPB, are sortase-anchored multidomain adhesins in *S. aureus* that interact with several mammalian targets. FnBPB binds plasminogen independently of fibrinogen via distinct lysine-rich sites, facilitating bacterial spread and immune evasion during infection. FnBPB dual binding capabilities as critical for *S. aureus* virulence and dissemination [144].

Clumping factors A and B (ClfA and ClfB) are high-affinity fibrinogen-binding adhesins in *S. aureus*, with ClfA also binding other glycoproteins, such as von Willebrand factor (vWF), through a non-covalently anchored vWF-binding protein [145]. Uniquely, ClfA exhibits force-sensitive adhesion, where weak bonds at low forces strengthen under high forces due to conformational changes, a catch-bond behavior that enables *S. aureus* to withstand shear forces in dynamic environments like blood flow [146]. Similarly, collagen-binding adhesin Cna helps *S. aureus* evade immune defenses, forming a "collagen shield" by binding collagen and C1q, which supports chronic infection by dampening immune responses, although Cna-negative strains spread more rapidly [147].

Surface proteins SasG in *S. aureus* and Aap in *S. epidermidis*, both possessing an LPxTG motif for cell wall anchoring, bind glycans with complex N-linked structures. SasG exists in two allelic variants: SasG-I and SasG-II, with SasG-II showing a broader ligand-binding capacity due to an arginine in its lectin domain which includes core 2 O-glycans [148]. Aap, SasG, and Pls (plasmin-sensitive protein) contain lectin domains that bind metal ions without the non-proline cis-peptide bond, suggesting an unconventional ligand-binding mechanism [149].

The serine-rich repeat glycoprotein (SRRP) SraP further enhances *S. aureus* adhesion by interacting with sialylated receptors through its Neu5Ac-binding lectin-like module [150]. Finally, SpA, another cell wall-anchored protein, has heparin-binding properties, and alongside numerous other surface proteins with potential heparin-binding capability, underlines the broad adhesion profile of *S. aureus* and the need for further studies to elucidate these interactions [151,152] (Table 9).

Shigella spp.

Shigellosis is an infectious disease caused by *Shigella* species, which primarily targets the digestive system. It typically presents symptoms such as abdominal pain, diarrhea, and fever. The genus *Shigella* consists of several species, each contributing to the overall disease burden in different regions of the world. *Shigella dysenteriae* preferentially adheres to colonic mucins, but this adhesion remains unaffected by pre-incubation with mucin monosaccharides. Although *S. dysenteriae* also binds to glycolipids, no specific glycan structures have been identified as its receptors [153].

S. flexneri engages in glycan–glycan interactions between its O-antigen polysaccharide (part of its polysaccharide) and the gangliosides GM1 and GM3 [154]. In serotype 2a, *S. flexneri* LPS specifically interacts with glycans from glycoprotein 2 (GP2), demonstrating its glycan-mediated adhesion capacity [155]. These interactions also involve sialyl Tn and Tn antigens present on MUC2 mucin [156]. Like many other bacterial species, including *E. coli, Shigella* also possesses type 1 pili that specifically target Man residues [157].

The type III secretion system (T3SS) attachment complex comprises the IpaB, IpaC, and IpaD proteins. IpaB and IpaC are responsible for forming pores in the membrane of eukaryotic cells. At the same time, IpaD plays a key role in the assembly of the complex by facilitating the incorporation of IpaB and IpaC [158]. IpaB interacts with CD44, a glycoprotein on epithelial cell surfaces that serves as a receptor for hyaluronic acid, suggesting a potential role for glycans in mediating this interaction [159]. Additionally, IpaB, along with IpaC and IpaD, facilitates *S. flexneri* invasion by interacting with the α5β1 integrin complex, although the precise contribution of glycans in these interactions remains to be elucidated [160]. Other potential adhesion mediators include IcsA (VirG) [161], the *sap* gene, which exhibits significant sequence similarity to the antigen 43 autotransporter of pathogenic *E. coli* [162], and OspE1/OspE2, which are activated by bile salt sensing through the T3SS [163]. However, the molecular details of their specific targets, including potential glycan involvement, remain unclear (Table 10).

Salmonella spp.

Salmonella species are primarily acquired through oral transmission and are responsible for four major clinical syndromes: enteric fever (typhoid fever), enterocolitis/diarrhea, bacteremia, and chronic asymptomatic carriage [164]. *Salmonella* infections rely on the ability of the bacteria to adhere to host cells to cause these syndromes. For example, *Salmonella enterica* serovar Typhimurium (*S.* Typhimurium) has been shown to recognize the glycan Galβ1–3GalNAc on Caco-2 cells, although the exact adhesins involved in this recognition process remain unidentified [165]. On the contrary, the presence of terminal GalNAc, through the action of glycosyltransferase β1–4*N*-acetylgalactosamin yltransferase 2, has been shown to have minimal impact on *S.* Typhimurium adhesion to epithelial cells [166]. Three key adhesins, type I pilus, plasmid-encoded fimbriae (Pef), and Std, have been characterized for their interactions with distinct oligosaccharide motifs (Table 11).

Type 1 pili, which mediate Man-sensitive hemagglutination and facilitate attachment to host cells, are present in *Salmonella enterica* serovars but are absent in *S. bongori*. Interestingly, the type 1 pili of *Salmonella enterica* serovar Gallinarum biovars Pullorum and Gallinarum were initially classified as type 2 fimbriae due to their inability to bind Man. This difference was later attributed to specific amino acid substitutions in the FimH protein compared to *S*. Typhimurium [167,168]. Later, nonsynonymous single nucleotide polymorphisms (nsSNPs) in

Table 9
This table lists glycans and monosaccharides recognized by *Staphylococcus aureus* and the corresponding literature.

Glycan/monosaccharide recognized	**Literature**
Sialic acid (Neu5Ac)	[150]
N-acetyl-d-lactosamine and 3′-sialyl-*N*-acetyllactosamine	[148]
Core 2 O-glycans	[148]
Heparin (disaccharide repeat consisting of GlcNAc and iduronic acid)	[151]

Table 10
This table lists glycans and monosaccharides recognized by *Shigella* spp. and the corresponding literature.

Glycan/monosaccharide recognized	Literature
GM1 and GM3	[154]
Glycans from GP2	[155]
Sialyl Tn and Tn Antigens	[156]
Man	[157]
Hyaluronic acid (disaccharide repeat consisting of GlcNAc and glucuronic acid)	[159]

Table 11
This table lists glycans and monosaccharides recognized by *Salmonella* spp. and the corresponding literature.

Glycan/monosaccharide recognized	Literature
Galβ1–3GalNAc	[165]
Man	[65,167,168]
α1–2Fuc	[171,172,174]
Le^x	[175,176]
Blood groups	[155]

FimH were identified, resulting in amino acid changes that affect its host-specific binding and facilitate the adaptation of *S*. Typhimurium to different hosts [169]. In *S*. Typhimurium, the FimH protein facilitates adhesion to enterocytes, while in *E. coli*, FimH preferentially binds to bladder epithelial cells [170]. In both species, glycoprotein 2 (GP2), uniquely expressed on the apical plasma membrane of M cells in the intestinal epithelium, is recognized by the type 1 pilus through Man-binding [65]. *S*. Typhimurium utilizes its Std pili to adhere to colonic epithelial cells by targeting α1–2Fuc found on N-linked glycans and mucus glycoproteins [171,172]. This adhesion is a crucial step in its infection strategy, which is further supported by its ability to metabolize elevated Fuc levels in the inflamed gut, enhancing growth and colonization, particularly following microbiota disruption [173,174]. Pef exhibits specific binding to the Le^x, predominantly expressed on crypt epithelial cells. This interaction suggests a potential role for Pef in facilitating *Salmonella* adhesion to the crypt epithelium in humans [175]. Finally, the pef operon, responsible for Pef production, is found on the virulence plasmid of *S*. Typhimurium. It is also present in *S*. Enteritidis, *S*. Bovismorbificans, *S*. Paratyphi C, and *S*. Choleraesuis, although two genes found in *S*. Typhimurium are missing [176].

Furthermore, one of the surface-exposed molecules on *Salmonella*, LPS, has been shown to target blood group antigens through glycan-glycan interactions in *S*. Typhimurium [155].

Neisseria gonorrhoeae

Neisseria gonorrhoeae, the bacterium that causes gonorrhea, is a major global public health problem, particularly because of complications that disproportionately affect women, such as pelvic inflammatory disease, ectopic pregnancy, infertility and increased susceptibility to HIV [177]. *N. meningitidis* can asymptomatically colonize the human oropharynx and, although rare, enter the bloodstream to cause invasive meningococcal disease, resulting in life-threatening conditions such as meningitis and septicemia, as well as other complications such as pneumonia, arthritis, urethritis, and conjunctivitis [178]. Whereas *N. meningitidis* is known to possess several well-defined adhesins that mediate interactions with host glycans, the specific adhesins and glycan interactions involved in *N. gonorrhoeae* adhesion are mostly unknown (Table 12). For example, the trimeric autotransporter adhesin NhhA (Neisseria hsf homologue) and NHBA (Neisserial Heparin Binding Antigen) in *N. meningitidis* bind to heparan sulfate [179–181]. Although

Table 12
This table lists glycans and monosaccharides recognized by *Neisseria* spp. and the corresponding literature.

Glycan/monosaccharide recognized	Literature
Heparan sulfate (disaccharide repeat consisting of GlcNAc and glucuronic acid with sulfate on hydroxyl groups)	[179–181, 185–187]
Le^x	[182]
sialylated Le^x	[182]
Lacto-*N*-neotetraose	[182]
Sialylated-lacto-*N*-neotetraose	[182]
Sialylated poly-*N*-acetyllactosamine	[183]
Syndecan 1 (heparan sulfate proteoglycan)	[188]
Chondroitin sulfate (disaccharide repeat consisting of GalNAc and glucuronic acid with sulfate on hydroxyl groups)	[182]

N. gonorrhoeae shares some adhesins with similar binding properties to *N. meningitidis*, it utilizes distinct mechanisms for adherence and invasion of male urethral epithelial cells. Notably, *N. gonorrhoeae* NHBA exhibits a stronger binding affinity for heparin than chondroitin sulfate and glucose 6-phosphate, unlike its *N. meningitidis* counterpart. Moreover, *N. gonorrhoeae* NHBA, but not that of *N. meningitidis*, interacts with Le^x, sialyl Le^x, lacto-*N*-neotetraose, and their sialylated variants [182].

The initial attachment in *N. gonorrhoeae* is facilitated by pili, with subsequent adherence steps leading to tighter binding mediated by "opacity-associated" (Opa) proteins responsible for the opaque phenotype of agar-grown colonies. In *N. meningitidis*, T4P bind to Basigin/CD147, a glycosylated transmembrane protein of the immunoglobulin superfamily, via sialylated poly-*N*-acetyllactosamine-containing N-glycans [183]. While direct evidence for *N. gonorrhoeae* T4P binding is still lacking, the PilC protein - identified as the tip-localized adhesin of T4P in both bacteria - has been shown to interact with closely related epithelial cell receptors [184].

Heparan sulfate proteoglycans, previously introduced as key mediators of adhesion in *Neisseria*, play a critical role in *N. gonorrhoeae* attachment, particularly through interactions with OpaA proteins that bind to syndecan receptors [185]. This interaction highlights the essential role of syndecans, particularly syndecans 1 and 4, in facilitating bacterial attachment and invasion by binding to the hypervariable region 1 of the OpaA protein [186,187]. The GAG chains of cell surface syndecan 1 (Sdc1) further enhance bacterial pathogenesis by promoting bacterial attachment to host cells. When bacterial adhesins bind to these Sdc1 chains, signals are transmitted through the highly conserved Sdc1 cytoplasmic domain, potentially leading to *N. gonorrhoeae* uptake into host cells [188].

Medium priority

Streptococcus pneumoniae, Group A and Group B Streptococci

Streptococcus pyogenes (Group A Streptococcus, GAS) [189] and *Streptococcus agalactiae* (Group B Streptococcus, GBS) [190] are important human pathogens known to cause a variety of infections, including throat and skin infections, as well as serious invasive diseases. *Streptococcus pneumoniae* is associated with several infections, including pneumonia, meningitis, bacteremia, and sinusitis [191]. GAS binds sialic acid residues on mucins during colonization, primarily through their outer surface M protein, a key virulence factor containing a LPxTG motif [192]. The M protein shows variability among GAS strains, and Rebecca Lancefield's M typing system, established in 1928, became the gold standard for serotyping. However, it has faced challenges due to limited antisera and high non-typability in tropical isolates. Instead, *emm* typing, based on sequence analysis of a portion of the M protein gene, now provides an alternative approach that closely correlates with traditional M serotyping [193,194]. This variability not only affects the accuracy of typing, but also affects the interactions of the M protein with host tissues [195]. Among the different *emm*-types, the M6, *emm*49 bind to GAGs, while M1, M3, M12 of this protein has a different binding affinity for ABO blood group antigens, lewis antigens and sialic acids [196,197]. The GBS surface alpha C protein contains a GAG-binding domain that has been shown to promote the bacterial penetration of the *Drosophila* blood-brain barrier as well as the adhesion to and the invasion of human brain microvascular endothelial cells [198]. Similarly, choline binding protein A (CbpA) interacts with factor H to enhance adherence and subsequent internalization of *S. pneumoniae* through GAGs [199]. Furthermore, GlcNAcβ1–3 Gal inhibits *S. pneumoniae* adherence to epithelial cells, although the specific adhesin(s) responsible for this interaction remain unidentified [200]. Notably, β-galactosidase BgaA and neuraminidase A NanA have lectin domains that enable them to act as adhesins independently of their enzymatic functions [201].

In GAS (PulA) and *S. pneumoniae* (SpuA), surface-anchored

pullulanases have glycogen-binding modules that allow multivalent interactions with glycogen. These interactions are mediated by pullulanase-associated CBM41 modules, which are common to starch/glycogen debranching enzymes of the GH13 family (based on the Carbohydrate-Active Enzymes database (CAZy)) [202]. Bacteria first enter alveolar cells after binding to specific ligand including glycans. Once inside, their ability to bind to glycogen allows them to degrade the polysaccharide and gain a metabolic advantage within the host [203,204].

Other adhesins have been identified, although less is known about their specific molecular targets. To date, SpeB from GAS has been shown to bind glycoproteins such as thyroglobulin, fetuin, mucin, asialofetuin, and laminin [205], while also functioning as a broad-spectrum protease capable of cleaving over 200 host proteins [206]. Several streptococcal adhesins target ECM proteins. For example, SfbI (Streptococcal fibronectin-binding protein I) in GAS binds to fibronectin [207], while LraI (lipoprotein receptor antigen I) in GBS, a lipoprotein, binds to laminin [208]. Srr1 and Srr2 a member of the MSCRAMM along with FbsA, FbsB, and FbsC, are surface-associated proteins encoded by GBS that bind to fibrinogen [209,210]. Similarly, the adhesin RrgA from a pilus protein found in multiple *Streptococcus* species, also targets ECM proteins [211]. A total of seven components are essential for the formation of this pilus, including the *rlrA* regulatory element, the backbone forming pilin (RrgB), RrgA, a minor pilin (RrgC), and three sortases (SrtC-1, SrtC-2, and SrtC-3) [212]. The ligand-binding vWFA domain of RrgA has two arm-like protrusions that form a U-shaped cradle composed of basic residues that may serve as a binding site for negatively charged glycan carbohydrates [211]. Interestingly, Spr1345 from *S. pneumoniae* R6 encodes a mucin-binding protein (MucBP), part of a group of surface proteins that promote bacterial adhesion to host mucins. The first MucBP, named Mub, was discovered in *Limosilactobacillus reuteri*, where it was identified as a high molecular weight protein with 14 repeats of the mucin-binding domain (MucBD) [213]. In contrast, Spr1345 is a low molecular weight MucBP containing only a single MucBD. In addition to this domain, Spr1345 has a proline-rich region and a C-terminal LPxTG motif that is recognized and cleaved by sortase [214]. The MucBD is predicted to interact with mucins and various polysaccharides such as hyaluronan, suggesting a potential specificity for the carbohydrate moiety of mucins [215].

In *Streptococcus sanguinis*, T4P plays a central role in adhesion, and their glycan-binding specificity suggests the possibility of similar lectin-mediated interactions in other *Streptococcus* species. The minor pilin PilA stabilizes another minor pilin, PilC, which contains a lectin module that specifically binds sialylated glycans, particularly those with an α2–3-sialyl linkage, such as 3′-sialyllactose and 3′-sialyl-*N*-acetyllactosamine. PilC can also recognize ligands such as ganglioside GD1a, oligosaccharides with the Sda antigen, and sulfated GAGs [216]. In *Streptococcus gordonii* and *S. sanguinis*, serine-rich repeat (SRR) adhesins - specifically Hsa, GspB, and SrpA - bind Neu5Ac/Neu5Gcα2–3 through their Siglec-like domains [217] (Table 13).

Table 13
This table lists glycans and monosaccharides recognized by *Streptococcus pneumoniae,* Group A and Group B Streptococci and the corresponding literature.

Glycan/monosaccharide recognized	Literature
Sialic acid	[192,196,197,216,217]
GAGs	[196–198]
ABO blood groups	[196,197]
Lewis antigens	[196]
GlcNAcβ1–3Gal	[200]
Glycogen	[202]
Mucins	[205,215]
GD1a	[216]
Sda antigen	[216]
Sulfated GAGs	[216]

Haemophilus influenzae

Non-typeable *Haemophilus influenzae* (NTHi) is a human-adapted pathogen that primarily infects the respiratory tract. It is a common cause of otitis media, community-acquired pneumonia, and exacerbations of chronic obstructive pulmonary disease (COPD) [218]. Its ability to interact with host glycan structures, especially sialic acid, enhances its adherence to epithelial cells (Table 14). NTHi lipooligosaccharides (LOS) have been shown to preferentially adhere to Lewis structures on host cell surfaces via glycan–glycan interactions. Interestingly, the removal of sialic acid from the LOS enhances bacterial adherence, highlighting the role of sialylation in modulating bacterial interactions with host cells [155]. The major NTHi adhesin Hia, a phase-variable autotransporter protein, acts as a dual-function lectin, binding with high affinity to human respiratory tract sialic acid glycan receptors, particularly Neu5Acα2–6Galβ1–4GlcNAc (2–6 SLN-Ac), via its BD1 domain [219]. Specific amino acid residues, including D618, A620, and R674 mediate this interaction. Additionally, the BD2 domain of Hia can bind the Neu5Acα2–3Galβ1–4GlcN- (2–3 SLN-Ac) epitope, and Hia expression in NTHi strains induces the formation of dense biofilms on epithelial cells. Other lectin adhesins, such as HMW1 and HMW2, play critical roles in the adherence of *H. influenzae* to sialylated glycan structures. They are trimeric autotransporters (TAA) with heavy molecular weight proteins. HMW2 shows a preference for 2–6 SLN-Ac and HMW1 favors 2–3 SLN, further underscoring the importance of sialic acid in *H. influenzae* pathogenicity [220,221]. Furthermore, outer membrane proteins P2 and P5 interact specifically with sialic acid-containing oligosaccharides on nasopharyngeal mucins, facilitating bacterial colonization [222,223]. Similarly, *H. influenzae* fimbriae (HIF) allows attachment to human respiratory mucins [224]. Other NTHi adhesins, although less well characterized in terms of their molecular targets, also play important roles in host interactions. One such adhesin is Hap, which binds to extracellular matrix components like collagen IV and laminin and serves as the primary ligand for fibronectin [225]. In addition, several other NTHi adhesins contribute to its adhesion capabilities. For instance, Protein E (PE) mediates adherence to both epithelial cells and vitronectin, while P4, a surface-associated lipoprotein is essential for binding to vitronectin and for the bacterium's survival in the middle ear [226].

Other pathogens no longer on the WHO 2024 list

Helicobacter pylori

The genome of *Helicobacter pylori*, a human gastric pathogen responsible for stomach ulcers and gastric cancer, encodes a diverse array of outer membrane proteins (OMPs) located in the bacterial cell envelope, which are classified into six groups: Hop (*H. pylori* OMPs), Hor (Hop-related), Hof (*Helicobacter* OMPs), Hom (*Helicobacter* outer membrane), iron-regulated OMPs, and efflux pump OMPs. Many *H. pylori* OMPs, particularly those in the Hop family, are predicted to function as porins or adhesins, aiding the bacterium in binding to the gastric mucosa [227,228] (Table 15). Notably, the blood group antigen–binding adhesin, BabA (HopS), the sialic acid-binding adhesin, SabA (HopP), and the lacdiNAc-binding adhesin, LabA (HopD) are known to recognize glycan residues [229–232].

Table 14
This table lists glycans and monosaccharides recognized by *Haemophilus influenzae* and the corresponding literature.

Glycan/monosaccharide recognized	Literature
Sialic acid	[155,219,221–223]
Lewis antigens	[155]
2–6 SLN-Ac, 2–3 SLN-Ac	[219,221]
Mucins (Human respiratory)	[224]

Table 15
This table lists glycans and monosaccharides recognized by *Helicobacter pylori* and the corresponding literature.

Glycan/monosaccharide recognized	Literature
Le^b	[239]
Blood group ABO glycans	[230]
α2–3 linked Neu5Ac	[232,246–248]
LacdiNAc	[231]

H. pylori infection begins via the oral route, where initial attachment can occur with salivary proteins such as MUC5B and the glycoprotein, deleted in malignant brain tumors-1 (DMBT1) [233–235]. Once in the stomach, *H. pylori* targets the gastric mucosa by interacting with mucins, secreted MUC5AC and membrane-bound MUC1 [236]. However, when *H. pylori* binds to MUC1, the bacteria are removed from the epithelial cell surface as MUC1 acts like a releasable decoy [237,238]. The BabA adhesin, was the first adhesin able to recognize carbohydrates described in *H. pylori* which binds to ABO/$Lewis^b$ histo-blood group antigens (Le^b) [239]. It is one of the 35 most highly differentiated genes across populations in 723 *H. pylori* strains isolated worldwide [240]. *babA* genomic diversity varies not only across populations but also within different regions of the human stomach in the same individual [241]. *H. pylori* strains expressing the BabA protein can be categorized as either "specialists" or "generalists" based on their ABO blood group antigen preferences. Specialist strains specifically bind to blood group O glycans, whereas generalist strains can bind to glycans from blood groups O, A, and B [230]. This distinction is due to a single amino acid substitution in the carbohydrate-binding domain of BabA. Ib specialists strains the position 198 is occupied by a leucine, making part of the carbohydrate-binding domain inaccessible for binding to larger glycans from blood groups A and B. In contrast, this position is occupied by a serine in generalist strains, allowing them to bind to glycans from all three blood groups [242]. Notably, significant differences in Le^b binding have been linked to the geographic origin of *H. pylori* strains. While some strains exhibited high levels of Le^b binding, others showed little to no detectable binding [243,244]. Further studies are needed to determine the molecular basis for the differential ability of different *H. pylori* strains to recognize histo-blood group antigens [245].

When *H. pylori* colonizes the human gastric mucosa, it triggers inflammation and alters the glycosylation of the host tissues, leading to the new expression of α2–3linked Neu5Ac, including sialyl-$Lewis^a$ (sLe^a) and sialyl-$Lewis^x$ (sLe^x) [232]. The SabA adhesin recognizes and binds to these glycans, which are carried on gangliosides identified as Neu5Acα2–3neolactohexaosylceramide and Neu5Acα2–3neolactooctaosyl ceramide [246]. Another protein secreted by *H. pylori*, HP0721, binds strongly to the gangliosides GD1a and GM3. However, HP0721 is not thought to mediate high-affinity adhesion but may instead contribute to bacterial colonization by facilitating the use of sialic acid as a nutrient source [247,248].

The most recent *H. pylori* adhesin discovered to bind carbohydrates is LabA, which can recognize the lacdiNAc motif (GalNAcβ1–4GlcNAc) on MUC5AC [231]. Interestingly, among several adhesins, only SabA and LabA were shown to be downregulated in response to lactate, mediated by the CheA/CheY signaling system [249]. The effect of lactate on microbial virulence is well documented, suggesting that LabA may play a role in *H. pylori* virulence, particularly through its involvement in the CheA/CheY system, which has been implicated in bacterial adhesion in other species [250,251]. However, structural analysis of LabA suggests that the lacdiNAc motif may not be its in vivo ligand, leaving the binding specificity to lacdiNAc residues unclear and requiring further investigation [252].

Campylobacter spp.

Campylobacter jejuni is a leading cause of gastroenteritis. In addition to acute infection, *C. jejuni* can trigger autoimmune disorders such as Guillain-Barré syndrome (GBS) and its variant, Miller Fisher syndrome. The development of GBS is attributed to molecular mimicry between gangliosides and the LOS of the bacterium, leading to an immune response that mistakenly targets the host's nervous system [253]. The number of *Campylobacter* spp. adhesins targeting glycans is limited in the literature (Table 16). However, *C. jejuni* is known to recognize fucosylated structures, specifically targeting α1,2-fucosylated carbohydrate moieties that contain the H blood group epitope, found on human tissues and in human milk [254,255]. *C. jejuni* exhibits the ability to bind to the major human intestinal mucin, MUC2, and can also swim toward it. This is partly driven by the presence of l-Fuc, which is metabolized via a metabolic cluster also found in *C. coli* [256–258]. Glycan array analyses have shown that *C. jejuni* interacts not only with Fuc but with Gal, sialic acid, Man, GlcN, and glycosaminoglycans [259]. Specifically, *C. jejuni* binds O-glycans via core 1, core 2, H antigen, and Lewis antigens (Le^b, Le^y, Le^x) [260]. Two adhesins mediate these interactions: the major subunit of *C. jejuni* flagella, FlaA, and the major outer membrane protein (MOMP) [260,261].

Like other bacteria, *C. jejuni* can bind to terminal Gal and GalNAc on human glycans via its LOS with glycan-glycan interactions, and it can bind to blood groups and Lewis antigens with high affinity. These terminal monosaccharides, when present on GAGs, can inhibit the bacterial binding [155].

Interestingly, a Gal-sensing chemoreceptor (initially named Tlp11 and renamed CcrG for *Campylobacter* ChemoReceptor for Gal) in *C. jejuni*, can sense MUC1 and increase bacterial adhesion, a process that the presence of free Gal in the medium can completely inhibit. Given this interaction, CcrG likely plays a key role in detecting host cell surface glycans, particularly those with Gal moieties, thereby enhancing bacterial adherence to host tissues [262]. Similarly, the chemoreceptor Tlp10 also recognizes glycan ligands, but has two ligand binding sites: Site A binds arginine, α-ketoglutarate, fumarate, and other non-monosaccharide ligands, while site B is specific for glycan ligands containing Man, Fuc, Rhamnose, sialic acid, and Gal residues. Tlp10 can bind complex host glycans, including terminal and intermediate residues of structures like fucosylated human ganglioside GM1 and the Le^a antigen [263].

Development of antibacterial adhesion

To develop effective carbohydrate and glycan mimetics as inhibitors of pathogen binding to host cells, it is essential to identify common glycans that serve as bacterial adhesin targets. The table below highlights key glycans shared by at least two of the listed bacterial species, emphasizing their potential as therapeutic targets (Table 17). These synthetic molecules, designed to mimic the structure of natural carbohydrates, are engineered to enhance binding affinity, stability, and specificity while remaining cost-effective and easier to manufacture than most natural glycans, which often require complex extraction and

Table 16
This table lists glycans and monosaccharides recognized by *Campylobacter jejuni* and the corresponding literature.

Glycan/monosaccharide recognized	Literature
H blood group epitope	[254,255,260]
Fuc	[256–258,263]
Gal	[259,262,264]
Sialic acid	[259,264]
Man	[259,264]
Glucosamine	[259,264]
GAGs	[259,264]
Core 1 and Core 2 O-glycans	[260]
Le^b, Le^y, Le^x, Le^a	[260,263]
Rha	[263]
GM1	[263]

Table 17
Summary of the main glycan receptors recognized by bacterial lectins and adhesins.

Glycan receptor type	Pathogen	Lectins
Heparan sulfate	*Neisseria gonorrhoeae*	NhhA, NHBA and OpaA
	Mycobacterium tuberculosis	HBHA
	Pseudomonas aeruginosa	Flagellum
Hyaluronic acid	*Mycobacterium tuberculosis*	Rv3194c
	Shigella spp.	IpaB
Sialic acid	*E. coli*	K99, F17bG, Ucl, Sfa
	Proteus spp.	Uca, MR/P
	Pseudomonas aeruginosa	Flagellum
	Staphylococcus aureus	SraP
	Shigella spp.	Serotype 2a, *S. flexneri* LPS
	Neisseria gonorrhoeae	NHBA, T4P
	Group A Streptococcus	M protein
	Streptococcus sanguinis	T4P
	Haemophilus influenzae	Hia, HMW1, HMW2
	Helicobacter pylori	SabA
	Campylobacter spp.	Chemoreceptor Tlp10
Gangliosides	*Pseudomonas aeruginosa*	Flagellum
	Campylobacter spp.	Tlp10
Blood groups	*E. coli*	F18 (FedF)
	Salmonella Typhimurium	LPS
	Campylobacter spp.	FlaA, MOMP
Mucins	*Pseudomonas aeruginosa*	LecA, LecB
	Haemophilus influenzae	HIF, P2, P5
	Streptococcus pneumoniae	SpeB, MucBP
Antigens Lewis	*Neisseria gonorrhoeae*	NHBA
	Haemophilus influenzae	LOS
N-acetylglucosamine	*E. coli*	F17 G fimbriae
	Streptococcus pneumoniae	–
Mannose	*Acinetobacter baumannii*	CsuA/BABCDE pilus
	E. coli	FimH
	Enterococcus faecium	SpaC
	Salmonella enterica	Type 1 pili
	Shigella spp.	Type 1 pili
Fucose	*Pseudomonas aeruginosa*	LecB
	Enterococcus faecium	SpaC
	Campylobacter spp.	Tlp10
	Salmonella Typhimurium	Std pili
Galactose	*Acinetobacter baumannii*	Ata
	Pseudomonas aeruginosa	LecA
	Campylobacter spp.	CcrG, Tlp10
Globotriaosylceramide	*E. coli*	PapG
	Pseudomonas aeruginosa	LecA
Lactotetraosylceramide	*Acinetobacter baumannii*	–
	E. coli	CFA/I pilus
LewisX	*Salmonella* spp.	Pef
	Neisseria gonorrhoeae	NHBA
Sulfated glycosaminoglycans	*Mycobacterium tuberculosis*	MUL_3720
	Streptococcus pneumoniae	PilC

The abbreviations represent: NHBA: Neisseria Heparin-Binding Antigen, NhhA: Neisseria hia/hemagglutinin adhesion, OpaA: Opacity-associated outer membrane protein, HBHA: Heparin-binding hemagglutinin, Rv3194c: Hyaluronan-binding adhesin, IpaB: Invasion plasmid antigen B, K99: Sialic acid-binding adhesin, F17bG: Fimbrial adhesin, Ucl: Uropathogenic E. coli fimbriae, Sfa: S-fimbriae, Uca: Uropathogenic cell adhesin, MR/P: Mannose-resistant Proteus-Like fimbriae, SraP: Sialic acid-binding adhesin in Staphylococcus aureus, LPS: Lipopolysaccharide, T4P: Type IV pili, M protein: Virulence-associated protein in Group A Streptococcus, HMW1/HMW2: High molecular weight adhesin 1/2, SabA: Sialic acid-binding adhesin, FlaA: Flagellin protein, MOMP: Major outer membrane protein, F18 (FedF): Fimbrial adhesin in E. coli, SpeB: Streptococcal cysteine protease, MucBP: Mucin-binding protein, LOS: Lipooligosaccharide, F17G: N-acetylglucosamine-binding fimbrial adhesion, CsuA/BABCDE: Chaperone-usher pilus system, SpaC: Pili-associated adhesin, Std: Fucose-binding fimbriae, Ata: Autotransporter adhesin, CcrG: Galactose-binding chemoreceptor, PapG: Galabiose-binding adhesion, CFA/I: Colonization factor antigen I, Pef: Plasmid-encoded fimbriae, MUL_3720: Sulfated glycan-binding adhesin, PilC: Pilus-associated adhesin.

purification processes. Notably, multivalent glycan mimetics display multiple carbohydrate motifs on a single backbone, significantly strengthening binding through multivalent interactions. This strategy effectively disrupts bacterial adhesion and holds great promise for the development of novel anti-adhesion therapies against bacterial infections [265]. Targeting the biosynthesis of adhesins also holds promise, as this would interrupt the production of critical binding molecules, impeding bacterial colonization at the source [266]. Another promising direction involves the design of multivalent glycoconjugates, which can simultaneously bind multiple bacterial adhesins to block adhesion effectively. Dendrimers, for example, have been developed to inhibit the FimH adhesin in *E. coli*, reducing bacterial attachment by occupying multiple binding sites at once [267]. An alternative approach could be to target the catch bond mechanism itself. Initially identified in the type I pilus, catch bonds have also been observed in other adhesins, including the type 3 pilus found in various Enterobacteriales [107]. In contrast, the Sdr adhesin from *S. aureus* utilizes a distinct "dock, lock, and latch" (DLL) mechanism. In this process, the target ligand first binds to a groove on the adhesin, followed by locking through specific protein domains, and finally a latching by an additional structural element that stabilizes the interaction, even under mechanical force [268,269]. The development of allosteric inhibitors to disrupt catch bonds and the DLL mechanism could provide a novel way to modulate bacterial adhesion without directly competing at the primary binding sites. For FimH, allosteric inhibitors could stabilize its open conformation, preventing the transition to the closed, high-affinity state under mechanical force. By binding to non-active regions, such small molecules can "lock" FimH in a low-affinity state, thereby reducing its resistance to force without directly targeting the mannose-binding site. For the SdrG DLL mechanism, allosteric inhibitors could target the domains responsible for locking and latching, thus preventing the structural changes required for stable binding even if initial docking occurs.

Surface sensing, or mechanosensing, plays a critical role in bacterial colonization by allowing cells to detect and respond to mechanical stimuli from surfaces [270]. This process is essential for bacterial pathogens to identify and bind to host surfaces, including glycans, which is a critical step in colonization. Targeting and disrupting surface sensing mechanisms can disrupt this process and prevent pathogens from colonizing host surfaces.

Intermediate hosts for transmission to humans

Understanding the interactions between humans, animals, and pathogens in shared environments is essential to the One Health framework, which emphasizes the interconnectedness of human, animal, and environmental health. This is particularly important in the context of bacterial pathogens that can be transmitted through contaminated fresh produce. While much attention has been paid to human-animal interactions, pathogenic bacteria also target a variety of glycans on intermediate hosts such as plants. However, this aspect of host-pathogen interactions remains underexplored in scientific literature. Among the few examples, in *E. coli*, the FimH adhesin can be expressed at low temperatures compatible with plant growth and has

been shown to specifically bind mannose-containing polysaccharides and plant-derived N-glycans [271]. Similarly, the Yad pilus of *E. coli* K-12 and the *E. coli* common pilus (ECP) are expressed at low temperatures and facilitate adhesion to plant cell walls through interactions with xylose and arabinan residues, respectively [272,273]. In addition, while the F9 pilus is known for its role in binding terminal Gal residues on mammalian tissues, it has also been found to interact with galactosylated hemicellulose in plant cell walls [274]. These examples highlight the versatility of bacterial adhesins in targeting glycans in different host types, including plants, and underscore the importance of expanding research on plant-bacteria interactions as part of the One Health framework. This could provide valuable insights into how bacterial pathogens spread and persist across environmental interfaces.

Perspectives and future research directions

To date, most studies investigating interactions between bacterial adhesins and glycoproteins have primarily focused on single glycan epitopes. However, a new paradigm is emerging that focuses on characterizing interactions between bacterial adhesins and glycan patches within glycoproteins, paving the way for an exciting new area of research. This approach highlights the importance of glycan landscapes, where clusters of multiple glycans coalesce to form patches that create a more relevant context for bacterial adhesion [275,276]. In these cases, terminal glycan epitopes may serve as a "barcode" recognized by bacterial adhesins. Such recognition requires highly glycosylated proteins, a feature particularly typical of secreted mucins, but this concept can also be extended to glycolipids or hybrid interactions between glycolipids and glycoproteins. This is particularly relevant during inflammation in mucosal tissues, where disruption of the mucus barrier may allow the co-existence of mucins and membrane-bound glycomolecules [277]. Studying the microbial biology of these glycan patches, including their specific arrangements and compositions, will provide valuable insights into how bacterial pathogens navigate and exploit the host environment. Future studies of glycan patch recognition by bacterial adhesins will require the integration of advanced experimental and computational approaches. The development of synthetic glycan libraries and engineered glycoproteins is essential to accurately mimic natural glycan landscapes. This is exemplified by a cell-based platform that displays human glycodomains with tunable structures and patterns of O-glycans, allowing precise manipulation of glycan configurations [278]. These developments will have to be performed in association with structural biology techniques such as X-ray crystallography and cryo-EM to reveal detailed adhesin-glycan interactions. Similarly, surface-based assays such as glycan arrays and surface plasmon resonance (SPR) are likely to be used for high-throughput binding analysis. Super-resolution microscopy and mass spectrometry-based glycomics, including MALDI imaging, could provide insight into the structure and composition of glycan patches. The development of molecular dynamics simulations will be needed to model the dynamic nature of adhesin-glycan interactions in such complex interactions. As an illustration, mucinases from human gut bacteria, such as *Akkermansia muciniphila*, cleave peptide bonds in mucins by recognizing adjacent O-glycans, specifically targeting bonds between contiguous (bis) O-glycans [279].

Another important aspect of enzymes is their effect on bacterial adhesion through the production of glycosyl hydrolases (GH) that modify exposed glycans. For example, *S. pneumoniae* encodes extracellular glycosidases that enhance adhesion by modifying host glycoconjugates to expose glycan receptors via the pneumococcal neuraminidase A (NanA) [280]. The study of bacterial adhesion is evolving, with new research perspectives highlighting the critical role of GH in modulating this process. Because GH can alter the structure and availability of glycan receptors on host tissues, they may significantly influence bacterial binding. Future studies should consider how the specific GH produced by different bacterial species might affect bacterial binding to host glycans.

Host glycans play a critical role in mediating bacterial adhesion and serve as receptors that many pathogens exploit to establish infection. Targeting these host-pathogen interactions offers a promising strategy to prevent bacterial colonization and reduce reliance on antibiotics. At the same time, bacterial glycoconjugates - such as capsular polysaccharides, lipopolysaccharides, and glycoproteins - are key virulence factors that not only facilitate adhesion but also help bacteria evade immune responses. These bacterial glycans represent valuable targets for vaccine development. Conjugate vaccines, which couple bacterial polysaccharides to carrier proteins to enhance immunogenicity, have proven successful against pathogens such as *S. pneumoniae* or *K. pneumoniae*. Extending these approaches to a broader range of bacterial glycoconjugates could strengthen our arsenal against multidrug-resistant infections [281].

CRediT authorship contribution statement

Clara Dessenne: Writing – original draft, Data curation. **Christophe Mariller:** Writing – review & editing, Visualization, Formal analysis. **Olivier Vidal:** Writing – original draft. **Isabelle Huvent:** Writing – review & editing, Writing – original draft. **Yann Guerardel:** Writing – review & editing. **Elisabeth Elass-Rochard:** Writing – review & editing, Writing – original draft. **Yannick Rossez:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

I have no conflicts of interest to declare, and the same applies to all associated authors.

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Data availability

Data will be made available on request.

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