Antibody-Dependent Enhancement of Bacterial Disease: Prevalence, Mechanisms, and Treatment

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ABSTRACT Antibody-dependent enhancement (ADE) of viral disease has been demonstrated for infections caused by flaviviruses and influenza viruses; however, antibodies that enhance bacterial disease are relatively unknown. In recent years, a few studies have directly linked antibodies with exacerbation of bacterial disease. This ADE of bacterial disease has been observed in mouse models and human patients with bacterial infections. This antibody-mediated enhancement of bacterial infection is driven by various mechanisms that are disparate from those found in viral ADE. This review aims to highlight and discuss historic evidence, potential molecular mechanisms, and current therapies for ADE of bacterial infection. Based on specific case studies, we report how plasmapheresis has been successfully used in patients to ameliorate infection-related symptomatology associated with bacterial ADE. A greater understanding and appreciation of bacterial ADE of infection and disease could lead to better management of infections and inform current vaccine development efforts.

KEYWORDS antibody, capsular polysaccharide, enhancement, Gram-negative bacteria, Gram-positive bacteria, lipopolysaccharide, proteases

Antibodies are a critical part of the human humoral immune response that aid in the elimination of pathogenic microorganisms via a range of mechanisms (1). This depth in function can be attributed to their fragment antigen-binding (Fab) and fully crystallizable (Fc) structural domains joined by a flexible amino acid stretch termed the hinge region (2, 3). To neutralize pathogens, the Fab region binds to antigenic structures, typically localized at the cell surface, preventing direct interactions with host cells. The Fab region can also bind bacterial toxins, preventing their interaction with host cellular receptors and neutralizing their activity. In addition to this, antibodies can recruit potent effector molecules through interactions with their Fc regions, initiating a variety of clearance mechanisms precluding pathogenic infection. The specific effector molecules recruited are dependent on class and subclass of antibody involved (4). Despite these well-characterized protective aspects, antibodies that instead amplify disease have also been described, through phenomena such as antibody-dependent enhancement (ADE) and vaccine-associated enhanced respiratory disease (VAERD).

ADE is best known for its role in viral infections; such observations have been reported for flaviviruses (5–7) and influenza viruses (8–10). Recently, viral ADE of infection has been of increased interest for its possible role in exacerbating coronavirus infections (11, 12). ADE of viral infection occurs when suboptimal antibodies (i.e., low affinity, concentration, and/or specificity) cannot completely neutralize the etiologic pathogen, thereby resulting in increased binding, uptake, and replication, leading to inflammation (11). Additionally, binding of these antibodies naturally activates cytokine release or complement cascade for host protection but, when unchecked, may result in a fatal chain of events due to persistent tissue damage coupled with chronic inflammation.

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TABLE 1 Antibody dependent enhancement of bacterial infections

Bacterial species	Disease model	Virulence enhancement	Proposed antibody virulence properties	Reference(s)
<i>In vitro</i> models				
<i>Streptococcus pneumoniae</i>	Human respiratory epithelial cells	Enhanced bacterial attachment	Virulence enhancement by antibody proteolysis	17
<i>Acinetobacter baumannii</i>	Human respiratory epithelial cells	Enhanced bacterial attachment	Antibody-mediated increase in adhesion	18
Mouse models				
<i>Acinetobacter baumannii</i>	Pneumonia	Increased mortality and bacterial burden	Antibody-mediated increase in adhesion	18, 135
<i>Neisseria gonorrhoeae</i>	Gonorrhea	Increased bacterial burden and duration of infection	Antibody-mediated serum resistance	19, 20
Enteric bacteria	Sepsis	Increased mortality	Antibody-mediated protection from bactericidal killing	21
Human cohorts				
<i>Neisseria gonorrhoeae</i>	Gonorrheal infection	Increased susceptibility	Antibody-mediated serum resistance	22
<i>Pseudomonas aeruginosa</i>	Bronchiectasis lung infections	Worse lung function	Antibody-mediated serum resistance	23

VAERD is a unique clinical syndrome first observed in the 1960s when whole-inactivated viral vaccines for measles and respiratory syncytial virus (RSV) were administered in children (13). Along with aberrant T cell responses (14), the use of a limiting dose or conformationally incorrect antigen in vaccines can result in the production of non-neutralizing antibodies (15). As mentioned previously, this generation of nonneutralizing antibodies runs the potential risk of binding pathogenic microorganisms—but not blocking or clearing them—allowing them to replicate or permit formation of immune complexes activating complement pathways associated with several inflammatory disorders (15).

In a few cases, antibodies that enhance bacterial infection and disease have been described, although the mechanisms underpinning this phenomenon are distinct from those for viral ADE. In this review, we first cover research highlights of ADE of bacterial infection in animal studies and human cohorts. We then discuss the proposed molecular mechanisms and review other instances where these mechanisms have been reported. Finally, we examine current therapies for ADE of bacterial disease.

ANTIBODY-DEPENDENT ENHANCEMENT OF BACTERIAL INFECTION

The first hints of a specifically induced serum factor that may enhance bacterial infection dates back to 1894. Pfeiffer and Issaef found that naive guinea pigs given serum from guinea pigs previously infected with *Vibrio cholerae* were more susceptible to intraperitoneal infection by the *Vibrio* species (16). However, it was not until later that a specific antibody was confirmed to enhance some bacterial infections (Table 1).

Antibodies that enhances bacterial infection have been demonstrated within a few *in vitro* and mouse model studies (Table 1). For *Streptococcus pneumoniae*, bacterium-specific antibody responses enhance bacterial attachment to respiratory cells (17). In a mouse model of *Acinetobacter baumannii* pneumonia, the passive immunization of a monoclonal antibody (MAb) specific for the capsule increased mortality and bacterial burdens in the blood, lung, and spleen (18). The presence of these antibodies was found to increase adhesion of the bacteria to respiratory epithelial cells (18). In a mouse model of *Neisseria gonorrhoeae* infection, passive immunization with a MAb toward the reduction modifiable protein (Rmp) abrogated the protective effects of the 2c7 MAb (19), causing both increased bacterial burden and duration of infection (20). Finally, preexisting serum IgG specific for enteric bacteria correlated with worse survival in a mouse model of sepsis induced by cecal ligation and puncture (21).

Evidence of antibodies that enhance bacterial infection in humans has been more difficult to discern. The anti-Rmp antibody responsible for enhancing mouse infection of *N.*

gonorrhoeae was also found to increase susceptibility to *N. gonorrhoeae* in a study of 243 adult women (22). Based on findings from our work, the presence of high titers of lipopolysaccharide (LPS)-specific IgG2 in serum is associated with worse lung function in patients with bronchiectasis and chronic *Pseudomonas aeruginosa* infection (23).

Although there are only a few cases with direct evidence of bacterial ADE, the mechanisms underlying these antibody-mediated pathologies have been described in a wide array of bacterial infections. Here, we will discuss the prevalence and potential mechanisms of bacterial ADE of infection, including antibody-mediated serum resistance, virulence enhancement by antibody proteolysis, antibody enhancement of adhesion, and antibody-mediated protection from phagocytosis.

ANTIBODY-MEDIATED SERUM RESISTANCE

The complement system is a vital part of the immune response against bacterial pathogens, consisting of multiple soluble factors acting in a cascade to either promote opsonophagocytosis or directly kill bacteria through pore formation and cell lysis (24). The complement system can be activated through three distinct pathways, (i) the classical, (ii) alternate, and (iii) lectin; however, all three converge to form the membrane attack complex (MAC) which can insert into the outer membrane of Gram-negative bacteria, leading to cell death. The classical pathway of complement-mediated killing requires the binding of a specific antibody to an antigen on the cell surface of pathogens. Bound antibodies recruit the C1q component, leading to the complement cascade and formation of the MAC (24).

Resistance to complement-mediated lysis, commonly known as serum resistance, is an essential virulence trait of many pathogenic bacteria as it allows survival in the bloodstream (25, 26). Bacteria have developed numerous virulence factors to assist them in resisting the bactericidal effects of serum (27). Briefly, Gram-positive bacteria are innately resistant to MAC insertion due to the thick layer of peptidoglycan on their cell surface (28). For Gram-negative bacteria, the production of polysaccharide capsule, O-antigen-positive lipopolysaccharide (LPS), or lipooligosaccharide (LOS) has been shown to be important for serum resistance by providing a steric barrier protecting the outer membrane from insertion of the MAC (29–31). In spite of this defined role, many O-antigen- or capsule-expressing strains still remain sensitive to serum killing (23, 32, 33). Recently, the roles of other proteins such as Lpp in *Escherichia coli* have been shown to be vital for resistance (34). Some species also reduce complement activation via recruitment of complement regulatory proteins within the host to their cell surface (35). Antigenic variation and the shedding of surface-bound complement factors also provide resistance by circumventing pathogen recognition mechanisms (27). Finally, some species are capable of offensive maneuvers in the form of enzyme secretion which bring about degradation/inactivation of complement components or inhibit the formation of MAC (36).

Antibody-mediated serum resistance seems paradoxical due to its accepted role in classically activated complement-mediated killing. However, in both *N. gonorrhoeae* and *P. aeruginosa* infection, the antibody associated with enhanced infection or disease has been shown to block or inhibit the complement killing of bactericidal sera. These “blocking antibodies” have now been described for many different species, including *Neisseria* spp., *Brucella* spp., *Salmonella* spp., *Proteus* spp., and *Klebsiella* spp. (Table 2). Descriptions of inhibitory sera date back to 1901, when the “Neisser-Wechsberg” phenomenon was described wherein deactivated serum taken from a rabbit repeatedly infected with *Vibrio metschnikovii* increased the bactericidal effect of normal serum of this strain in moderate amounts but inhibited the bactericidal effect when mixed in large amounts (37). This inhibiting factor was shown to be specific, as it was able to be adsorbed out of the sera using the homologous strain (38). Below, we detail the bacterial diseases for which these antibodies have been described.

Meningitis: *Neisseria meningitidis*. In the 1940s, the first specific description of a factor in humans that blocked serum killing of a bacterial strain was reported. Serum

TABLE 2 Prevalence of antibody-mediated serum resistance in bacterial infection

Species	Disease	Organism(s) reported	Antigen	Antibody subtype	Reference(s)
<i>Actinobacillus pleuropneumoniae</i>	Respiratory disease	Pigs, guinea pigs	LPS	IgG	90
<i>Brucella</i> spp.	Brucellosis	Cattle, pigs, rabbits	LPS	IgA/IgG2	70, 75, 76
<i>Burkholderia cepacia</i>	Cystic fibrosis	Humans	Unknown	Unknown	136
<i>Escherichia coli</i>	Pyelonephritis, urosepsis	Humans	LPS	IgG, IgG2	78, 82
<i>Haemophilus influenzae</i>	NTHI	Humans	Unknown	IgA	92
<i>Klebsiella</i> spp.	Pyelonephritis	Humans	Unknown	Unknown	77, 78
<i>Neisseria gonorrhoeae</i>	Gonorrheal disease	Humans	LOS	IgA	60
			Rmp	IgG	65, 66
<i>Neisseria meningitidis</i>	Meningitidis	Humans, rabbit, guinea pig, horse	Capsule	IgA, IgG	39, 40, 137
			Lip H.8/Laz	IgA	46
			Pili	IgA	48
<i>Proteus mirabilis</i> and <i>P. morganii</i>	Pyelonephritis	Humans	LPS	IgG	80, 81
<i>Pseudomonas aeruginosa</i>	Pyelonephritis, lung infections	Humans	LPS	IgG2	83–85
<i>Salmonella enterica</i>	Various	Humans	LPS	IgG, IgA, IgM	86–89
<i>Serratia marcescens</i>	Bacteremia	Humans	LPS	IgG	50

samples taken from patients two weeks after their initially reported infection with *Neisseria meningitidis* was unable to kill a serum-sensitive strain, in direct contrast to sera taken during the acute phase of infection (39). These convalescent-phase sera were also able to block the killing of otherwise bactericidal normal human sera (NHS). A similar blocking factor was found in multiple patient cohorts (40, 41) and eventually identified as IgA1 binding to capsular polysaccharide of group C meningococcus (42). Adsorbing out all IgA restored bactericidal killing (41), whereas adsorption of all antibody specific for the capsule (42) removed both the inhibition and bactericidal activity, suggesting anti-capsule IgG promoted cell lysis (42). Blocking IgA specific for capsule of various serotypes of *N. meningitidis* has since been reported in multiple human cohorts (43, 44). Finally, evidence for an anti-capsule IgG antibody that inhibits alternative pathway complement-mediated killing was found in two C2-deficient sisters. One of these sisters when vaccinated with tetravalent meningococcal vaccine (containing capsular polysaccharides from serogroups A, C, W-135, and Y) developed an antibody response that blocked alternative pathway-mediated killing of serogroup W-135. IgG was identified as the blocking antibody and was found to inhibit killing of the W-135 serogroup strain but not a serogroup C strain (45). In contrast to the studies above, IgA was not shown to be involved in the inhibition (45).

Antibodies that inhibit complement-mediated killing also target other outer membrane structures of *N. meningitidis*. The serogroup B meningococcal capsule is not immunogenic; however, blocking antibodies have been identified against lipoproteins expressed by these strains. The serum samples from 17 healthy individuals were tested for their ability to kill a serogroup B *N. meningitidis* strain, finding variable killing throughout. Three of the four serum samples with low bactericidal activity were able to block bactericidal killing; however, they were not able to inhibit the killing of the strain by all bactericidal sera. The inhibition was found to be IgG3 specific for two lipoproteins: Lip/H.8 and Laz (46). The aforementioned lipoproteins contain almost identical pentapeptide repeats ($\times 15$ and $\times 8$, respectively), and expression of both was required for maximal blocking. Bactericidal activity was able to be restored in sera by adsorbing out these blocking antibodies with synthetic peptide containing the pentapeptide repeats (46).

In humans, $\alpha 1,3$ -galactosyl antibodies (anti-Gal) are ubiquitously expressed, making up approximately 1% of total circulating IgG (47). Anti-Gal IgM, IgG, and IgA were found not to bind the LOS of *N. meningitidis* but bound to the pili of some strains (48). Total serum anti-Gal Ig was found to inhibit complement-mediated killing of pilus-producing *N. meningitidis* strains. When purified, serum IgA1 and secretory IgA inhibited killing, whereas purified anti-Gal IgG did not (48). Notably, anti-Gal has also been found to bind to LPS of enteric bacterial species such as *Klebsiella*, *Escherichia*, *Salmonella* (49), and *Serratia* (50).

Disseminated gonococcal infection: *Neisseria gonorrhoeae*. Antibody has long been shown to be necessary for complement-mediated killing of *N. gonorrhoeae*. NHS contain bactericidal IgM antibody that can target and kill serum-sensitive isolates of *N. gonorrhoeae* (51, 52). Strains that cause disseminated gonococcal infection are overwhelmingly serum resistant to NHS (53) but have been shown to be killed by the induction of specific antibodies in serum from convalescent patients (54, 55). In some cases, NHS were found to contain specific IgG antibodies that were able to block the bactericidal effects of both rabbit complement and convalescent-phase sera (56–58). These inhibitory antibodies have been found to be specific for either LOS or outer membrane proteins of *N. gonorrhoeae*. Antibody to LOS, primarily IgM (51, 59), has been shown to be responsible for a major proportion of bactericidal activity against *N. gonorrhoeae* (60, 61). In contrast, IgA specific for *N. gonorrhoeae* LOS isolated from pooled NHS was shown to block the bactericidal killing of IgG-mediated killing of the bacterium (60).

The best-characterized gonococcal antibody that inhibits complement killing is specific for an outer membrane protein: the reduction modifiable protein (Rmp, protein III). Antibody to Rmp has been shown to increase bacterial burden in a mouse model as well as act as a biomarker for susceptibility to *N. gonorrhoeae* in humans (20, 22). Rmp is a 236-amino-acid (aa) protein that is physically associated with the porin Por and is highly conserved within the genus *Neisseria* (62–64). Rmp is ubiquitously expressed in *N. gonorrhoeae* and demonstrates robust immunogenicity (65). IgG specific for Rmp was shown to inhibit bactericidal killing by protective antibodies, whether purified from human sera (65) or as a monoclonal antibody (66), although only one of two monoclonal antibodies directed against Rmp promoted the inhibitory effect (66). Bactericidal activity was able to be restored in nonkilling serum from convalescing patients by selectively adsorbing out the inhibitory anti-Rmp antibody. Recently, antibodies with higher bactericidal activity against *N. gonorrhoeae* have been induced by using a Rmp deletion strain (67). Rmp does exist in *N. meningitidis* (class 4 outer membrane protein), but the role of anti-Rmp antibodies in bactericidal killing of that species is unclear. One study identified anti-class 4 antibodies that blocked killing of the strain in one individual (68); however, antibodies specific for class 4 induced by a meningococcal outer membrane vesicle vaccine did not inhibit complement-mediated killing (69).

Brucellosis: *Brucella melitensis*, *B. suis*, and *B. abortus*. Brucellosis is the leading cause of zoonotic infection in humans worldwide and is caused by multiple bacterial species in the genus *Brucella*. *Brucella* spp. are small Gram-negative facultative intracellular coccobacilli, with four species known to have moderate to significant pathogenicity in humans: *Brucella melitensis* (sheep), *Brucella suis* (pigs), *Brucella abortus* (cattle), and *Brucella canis* (dogs). High titers of specific antibodies to *Brucella* species, likely serum IgA, are known to inhibit agglutination reactions (53, 64, 70, 71); however, a blocking factor of complement-mediated killing was simultaneously being described. In 1945, Huddleson and colleagues (72) showed that fresh plasma from cattle infected with *B. abortus* was not able to kill the bacteria when given a source of complement. In addition, this plasma inhibited the action of bactericidal plasma when mixed and was suggested to be antibody (72). Similarly, guinea pigs infected with *Brucella* had serum that was bactericidal seven days postinfection but unable to kill the strain 30 days postinfection (73). The bactericidal activity of fresh rabbit blood was also found to be inhibited when rabbits were immunized extensively with *B. abortus* (74). Analysis of rabbit hyperimmune serum indicated that IgA was primarily responsible for the bactericidal inhibition, with addition of IgA blocking the bactericidal effect of IgM or IgG isolated from the sera (75); however, the role of other antibody isotypes could not be ruled out.

The process behind serum bactericidal inhibition in cattle was comprehensively studied by Corbeil et al. (70), where the authors investigated the differences in killing of smooth (O-antigen expressing) and rough (O-antigen negative) strains of *B. abortus* after infection or immunization with either strain. When specific antibodies were present, killing of the rough strain by serum was increased. In contrast, as specific antibodies increased for the smooth *B. abortus*, killing of that strain in serum significantly

decreased (70). Antibodies involved in the killing inhibition were identified as IgG1 and IgG2, with IgG2 driving significantly more inhibition (70). Other studies have confirmed the blocking factor in bovine serum as IgG and suggested that antibody, under certain conditions, may actually promote establishment of bovine brucellosis (76).

Pyelonephritis: *Escherichia coli*, *Proteus mirabilis*, *Proteus morganii*, and *Klebsiella aerogenes*. Antibodies that block complement-mediated killing have also been described in pyelonephritis for a range of bacterial species, including *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella* spp. (77). In each case, patient sera blocked the ability of NHS to kill the cognate strain in a serum- and strain-specific manner.

In 1972, nine of 48 female patients with urinary tract infections were found to have a serum factor that inhibited NHS killing of their cognate strain (78, 79). Of the nine patients, eight were afflicted with pyelonephritis. Strains isolated from patients with this defect included *E. coli* serotypes O2, O4, O7, and O75, *Proteus morganii*, *Proteus mirabilis*, and *Klebsiella* spp. (78). This inhibitory factor was investigated in detail for the two patients infected with *Proteus* spp. and confirmed to be due to IgG specific for LPS (80). Adsorbing out all IgG, or antibody specific for LPS, was sufficient to restore bactericidal activity of the serum (81). Finally, we recently found that 24% of 45 patients with *E. coli* urosepsis infection had antibodies that inhibited serum killing. These antibodies were IgG2 specific for LPS of the *E. coli* strain. Isolates taken from patients with these serum-killing inhibitory antibodies were more sensitive to NHS, suggesting the presence of these antibodies was required for these strains to survive in the bloodstream (82).

Bacterial lung infections: *Pseudomonas aeruginosa*. Recurrent and chronic bacterial lung infections commonly affect those with bronchiectasis, cystic fibrosis (CF), and chronic obstructive pulmonary disorder. *P. aeruginosa* is a major cause of morbidity and mortality in these diseases and, once infection is established, is exceedingly difficult to eradicate. The first reported case of a blocking serum factor toward *Pseudomonas* was Waisbren and Brown's work (77). By investigating the sera of two patients with chronic *P. aeruginosa* infection, the blocking factor was identified as IgG and was able to be specifically adsorbed from the serum by using the cognate strain isolated from the patient (83). In a study investigating 42 patients with CF and *P. aeruginosa* infection, six patients of the cohort had serum that was unable to kill their autologous strain, even though it was sensitive to NHS killing (84). Additionally, these sera were able to kill heterologous strains of *P. aeruginosa* from other patients, suggesting the presence of patient-specific blocking antibodies in these sera (84).

The nature of blocking antibodies to *P. aeruginosa* was investigated in our study looking at 29 patients with bronchiectasis and chronic *P. aeruginosa* infection (85). Six of these patients had serum that was unable to kill their cognate strain, despite the isolates being sensitive to NHS killing. As little as 6% of patient serum added to NHS was able to completely inhibit complement-mediated killing. "Inhibitory sera" had significantly higher binding of IgG2 to their autologous strain, and specifically removing these IgG2 antibodies from the sera restored bactericidal activity. Conversely, reintroducing these purified IgG2 antibodies to NHS inhibited complement-dependent killing. Furthermore, antibody specific for the O-antigen component of LPS, but not lipid A, inhibited complement-mediated killing. Thus, IgG2 specific for the O-antigen was responsible for inhibiting complement-mediated killing. Importantly, patients with "inhibitory antibodies" had significantly worse lung function than patients with normal killing serum (23).

Salmonella infection: *Salmonella enterica* serovar Paratyphi B and *S. Typhimurium*. The first reported case of serum killing inhibitory antibodies against *Salmonella* spp. was in 1953, when the presence of excess antibodies to *Salmonella* R antigen (LPS core) was shown to block serum bactericidal activity (86). The study by Waisbren and Brown also reported two patients with inhibitory antibodies to their infecting *Salmonella* strain; an *S. Paratyphi* B strain from a patient suffering peritonitis and a rectus abdominus muscle abscess, and an *S. Typhimurium* strain from a patient suffering septicemia and a splenic abscess (77).

The first detailed study of an inhibitory antibody toward *Salmonella* was in 2010 when MacLennan and colleagues investigated a cohort of HIV-infected African adults

for their serum's ability to kill two *S. Typhimurium* strains, one resistant to NHS and one sensitive (87). Within this cohort, 58% of serum samples were not able to kill the sensitive strain, while 28% had lower bactericidal activity than the NHS of the resistant strain. A high titer of anti-*S. Typhimurium* IgG correlated with less bactericidal killing by the patient sera. The nonkilling sera were able to inhibit the action of NHS. The blocking factor was identified as IgG specific for *S. Typhimurium* LPS (87). Bactericidal activity was restored in patient sera by either adsorbing out the LPS-specific IgG or deleting O-antigen expression on the surface of the *Salmonella* strain. In contrast, antibodies targeting outer membrane proteins were found to be bactericidal (87).

In an analysis of 49 healthy adult serum samples, it was found that 48 had robust killing of an *S. Typhimurium* strain, with antibodies specific for LPS identified as important for the bactericidal activity (88). The single serum unable to kill the strain was found to contain inhibitory antibodies, correlating with anti-LPS IgM. The serum also led to less complement deposition on the bacterial strain. Thus, anti-LPS antibody was found to both promote and inhibit complement-mediated killing (88). This result was supported when it was later shown that any antibody specific for the LPS was able to inhibit complement-mediated killing, although IgA and IgG2 had the strongest association (89). The anti-LPS IgG, when sufficiently diluted, was found to be bactericidal; however, when concentrated from NHS, it resulted in the blocking of complement-mediated killing (89).

Individual cases: *Actinobacillus pleuropneumoniae* and *Haemophilus influenzae*.

Actinobacillus pleuropneumoniae is a Gram-negative encapsulated coccobacillus that causes acute to chronic respiratory diseases in swine worldwide. An antibody that inhibited complement-mediated killing of the strain was identified in normal swine serum and hyperimmune swine and guinea pig serum. The antibody was IgG specific for *A. pleuropneumoniae* LPS (90).

Nontypeable *Haemophilus influenzae* (NTHI) is a nonencapsulated Gram-negative commensal of the human nasopharynx. However, when present in the lower respiratory tract, it can become an important pathogen associated with conditions such as bronchitis, bronchiectasis, pneumonia, and chronic obstructive pulmonary disease (91). IgA, when purified from four of five patients with NTHI infection, inhibited the bactericidal activity of NHS or their own serum to kill their cognate strain (92). Although the IgA is specific for the NTHI strains, the precise target of the inhibitory IgA remains unknown.

Mechanisms underlying antibody-mediated serum resistance. Antibodies that inhibit the complement-mediated killing of bacteria can belong to various isotypes: IgA, IgM, IgG, IgG1, IgG2, and IgG3 (23, 42, 46, 70, 89). Additionally, these antibodies are specific for a variety of outer membrane structures such as LOS, LPS (core and O-antigen), capsule, lipoproteins, and outer membrane proteins (Table 2). Thus, there are likely multiple mechanisms underpinning the antibody-mediated inhibition. However, there are many similarities between the descriptions of antibody-mediated serum resistance that may be informative.

In many of the cases reviewed here, the antibodies required for complement resistance bind either LPS or LOS. In the case of *P. aeruginosa*, the antibodies specific for the O-antigen but not the lipid A/core of the LPS were found to be responsible (23). This is reinforced by studies where the inhibition is only found against smooth strains expressing O-antigen (70, 87). We and other groups have previously proposed two possible mechanisms of complement inhibition (23, 87). In both, high titers of antibody bind to the O-antigen of LPS and then exert their inhibitory effect either by (i) activating and depositing complement away from the bacterial membrane or (ii) creating a physical antibody blockade that prevents access of protective antibody and MAC to the cell surface. Evidence currently favors the latter explanation, where multiple studies have found the inhibition of complement-mediated killing to be dependent on high titers of the antibody. In *N. meningitidis*, if enough IgA was present to form a "blockade," no amount of IgM could restore bactericidal activity (93). This antibody has been shown to bind and activate MAC formation (23, 87); however, MAC activation is likely not required for complement resistance, as one study determined that removal of the Fc

FIG 1 Mechanism of cloaking antibody. (A) High-titers antibodies specific for the O-antigen of LOS/LPS form a steric barrier, preventing MAC insertion into the bacterial membrane. (B) Low titers of O-antigen specific antibody do not prevent access to the membrane for both protective antibody and MAC. (C) Lack of O-antigen target allows protective antibody and complement to access bacterial membrane.

portion from IgA1 did not affect the inhibition (42). Finally, many isotypes of antibody with disparate complement activation have been found to inhibit serum killing.

Only one study has found IgM to inhibit serum killing (89), with the majority of evidence indicating that IgM toward LPS is bactericidal in serum (51, 54, 75, 93, 94). We hypothesize that this may be due to the pentameric structure of IgM, which may interfere with the close packing of the antibody required to form the protective barrier. IgM typically has a lower affinity for antigens than other isotypes of antibody. As inhibitory antibodies need to block access of MAC to the membrane, we hypothesize that lower-affinity antibodies may be unable to block this insertion. Thus, we propose a mechanism of action where antibodies at a high titer bind to an abundant antigen that is distal from the cell surface. These antibodies completely cloak the bacteria, creating a physical barrier that prevents MAC insertion into the membrane (Fig. 1A). Antibodies at a low titer in serum cannot cover the entire surface of the bacterium, leading to bactericidal activity (Fig. 1B). Additionally, removal of the target epitope restores complement killing (Fig. 1C). This mechanism could apply to capsule, LPS, LOS, or any antigen that is numerous distal from the cell surface. Differences in the antibody titer or abundance of an antibody target may also explain differences in bactericidal effect.

Antibodies that protect bacteria from complement-mediated killing using this method have previously been termed inhibitory, blocking, or paradoxical antibodies; however, all these terms are broad or already have multiple uses in the field. We propose that these be termed “cloaking antibodies,” which describes the mechanism of action: complete coverage that gives protection and is distinct from these other aforementioned terms.

Finally, proteins have also been identified as targets for antibodies that inhibit complement-mediated killing: mainly Rmp from *N. gonorrhoeae* and Lip/H.8 from *N. meningitidis*. The mechanisms underlying the antibody inhibition are disparate. For Rmp, antibody binds and promotes complement deposition but does not lead to killing. It also can block the bactericidal action of protective antibodies. It is thought that the presence of the anti-Rmp antibody recruits complement proteins away from bactericidal sites of the *N. gonorrhoeae* to nonbactericidal sites (58). Whether this is due to steric hindrance, as with cloaking antibodies, has yet to be determined. Anti-Lip/H.8 antibodies differ in that their presence reduces complement activation (specifically C4), and although the antibodies are able to block the action of some protective MAbs, they are not able to inhibit the bactericidal action of a MAb to anti-PorA, possibly because PorA is a major and abundant porin of the *N. meningitidis* membrane (46). Thus, blocking by anti-Lip/H.8 antibodies is due to an overall reduction of complement activation and can be overcome by protective antibodies.

Antibody-mediated serum resistance and disease enhancement. The causal link between antibody-mediated serum resistance and enhancement of infection is clear in diseases that require serum resistance, such as bacteremia, urosepsis, and meningitis. The presence of the antibody allows otherwise serum-sensitive strains to survive in blood, leading to a higher burden of disease. Indeed, in *E. coli* urosepsis, the isolates taken from patients with high titers of cloaking antibodies were more sensitive to NHS killing, suggesting that the presence of these antibodies was required for the infection to survive in blood (82). In the case of facultative intracellular *Brucella*, some authors have speculated that protection from complement killing, while still promoting opsonophagocytosis, may facilitate higher infection of phagocytic cells between lysis/infection cycles (76).

The link between cloaking antibody and disease severity in lung infections, such as those shown in *P. aeruginosa*, is less obvious, where complement killing is not a main defense against infection in the lung. Lung damage in chronic *P. aeruginosa* lung infections is usually due to increased inflammation (95, 96). There are many ways antibodies may increase inflammation, including increased C5a generation as MAC is activated (97), the glycosylation state of the antibody (98), or differential Fc receptor activation (99). Antibody to LPS has also been shown to inhibit alveolar phagocytosis of *P. aeruginosa* (see below). Any one of these mechanisms may be responsible for the association with worse lung function.

Finally, although cloaking antibodies are associated with worse disease in many bacterial infections, it is important to note that antibodies to LPS, LOS, or capsule are protective in many of the diseases discussed above and are core components of current vaccines or vaccines under development (100–104). These antibodies are protective through various mechanisms such as by preventing adhesion of the bacteria in the gastrointestinal tract (105). Despite this, vaccine development efforts should also include consideration of the possibility of these antibodies enhancing bacterial infections, as it may also explain previous cases where LPS-based vaccinations have led to worse clinical status in some patients (106, 107). Finally, it is worth remembering that the serum of many mouse strains is unable to kill various Gram-negative bacteria by complement-mediated lysis (108, 109); thus, the role of serum resistance may not be accounted for in many models.

VIRULENCE ENHANCEMENT BY ANTIBODY PROTEOLYSIS

To counteract host immune pathways, bacterial pathogens have evolved to express and secrete proteases that target antibodies, preventing normal immunoglobulin effector function (110–112). Conceivably, this targeted cleavage of antibodies by bacterial proteases may represent a distinct mechanism for exacerbating bacterial disease. In several examples, pathogenic bacteria that produce IgA proteases are predominantly associated with colonization of mucosal surfaces (113, 114). The capability to evade these IgA-dominant mucosal sites provides a fitness advantage for these pathogens. As an example, in a study by Weiser et al. (17), the authors found specific antibody responses to the bacterium *S. pneumoniae* (pneumococcus) can enhance infection. This study found that a secreted bacterial protease cleaves IgA1 that has specificity to capsular polysaccharide (CPS). Rather than the widely accepted function of IgA1 inhibiting adherence to pharyngeal epithelial cells, the presence of the antibody instead significantly augmented adherence *in vitro*. The authors found that the IgA1 protease specifically cleaved antigen-bound CPS-specific IgA1. This specific cleavage resulted in localized “unmasking” of the capsule, allowing the not normally readily accessible ChoP surface ligand, a choline-containing molecule (phosphorylcholine), to interact with the receptor for platelet-activating factor (rPAF) on cells in the infected host, consequently allowing bacterial cell adherence. The authors considered that such an antibody-mediated mechanism would result in the ability of pneumococcus to persist on mucosal surfaces of the host respiratory tract.

A mechanism instead exploiting the hinge region for proteolysis has also been observed for immunoglobulin IgG. The extracellular secreted proteases glutamyl

TABLE 3 Bacterial proteases specific for immunoglobulins

Protease name	Pathogen	Immunoglobulin protease target	Reference(s)
IgA protease	<i>Haemophilus influenzae</i> type B	IgA1	124, 125
IgA protease	<i>Neisseria gonorrhoeae</i>	IgA1	135, 138
IgA protease	<i>Neisseria meningitidis</i>	IgA1	139, 140
IgA protease	<i>Streptococcus pneumoniae</i>	IgA1	17, 114
LasB (elastase, pseudolysin)	<i>Pseudomonas aeruginosa</i>	IgG1	122, 123
ZapA (mirabilysin)	<i>Proteus mirabilis</i>	IgG1/IgG2/IgA1	141–143
GluV8 (glutamyl endopeptidase I, SspA)	<i>Staphylococcus aureus</i>	IgG1	115, 144, 145
IdeS (immunoglobulin-degrading enzyme of <i>Streptococcus</i>)	<i>Streptococcus pneumoniae</i>	IgG1	116, 119
Dentilisin (PrpP, trepolisin)	<i>Treponema denticola</i>	IgG1	146

endopeptidase V8 (GluV8) of *Staphylococcus aureus* and immunoglobulin-degrading enzyme (IdeS) of *Streptococcus pyogenes* (115, 116) have been shown to cleave within the hinge region of IgG molecules (of the CH2 linker), disabling binding to host Fc receptors. Several other groups have reported that even a single cleavage in this region is able to abolish binding to Fc receptors (117). Interestingly, cystatin C, a host cysteine protease inhibitor, is “hijacked” and instead acts as cofactor for bacterial IdeS and accelerates IgG cleavage (118, 119). Mechanistically, the literature is not clear, but perhaps cleavage of the IgG immunoglobulin serves two functions in precluding bacterial clearance by not only impeding the regulation of a conducive immune response by Fc receptors binding but also masking epitopes to other components of the host immune system. A similar tactic to evade host immune responses by many pathogenic bacterial species is to express cell surface proteins (e.g., protein A of *S. aureus* and Eib proteins of *E. coli*) that bind antibodies outside the Fab region of IgG so that these antibodies are incorrectly orientated and therefore functionally impaired from eliciting an immune response (120, 121). Altogether, the presence of antibody in these scenarios would instead actively enhance protection of the bacteria.

From these discussed studies, it becomes clearer that the exploitation by proteolysis of immunoglobulin is a common strategy of pathogenic bacteria (Table 3). The evolution of such different protease family classes (serine-, cysteine-, and metalloproteases) shows the viability of such a strategy and how this may contribute in such distinct ways for a mechanism of bacterial ADE infection. Furthermore, it is worth mentioning that some proteases have a broad substrate range (i.e., LasB of *P. aeruginosa*) (122, 123) or are only expressed in specific disease states (IgA1 protease of *H. influenzae*) (124, 125). Thus, further research that uses a combination of mutational and *in vivo* infection studies would be required to dissect the precise role these proteases play in contributing to antibody-mediated enhancement of bacterial infection.

ANTIBODY-MEDIATED INCREASE IN ADHESION

A reported feature of some clinically relevant pathogens is the ability to shed or modulate their capsular polysaccharide (CPS) layer (126–128). The function of this dynamic process of capsule shedding or restructuring has been described for the evasion of host immune defenses, potentially providing insight to explain antibody-mediated enhancement of bacterial infection. Wang-Lin et al. (18) reported that a mechanism of ADE exists for *A. baumannii* infection in a mouse pneumonia model. The authors reported the development of a therapeutic monoclonal antibody and assessed its ability to induce protective immunity against clinical strain *A. baumannii* AB99. The designed IgG3 monoclonal antibody—8E3—was developed for specificity toward serotype K2 CPS of *A. baumannii* AB99. However, *in vivo* immunization resulted in AB99-infected mice with increased mortality accompanied by significant increases in bacterial loads in blood, lung, and spleen samples. The authors then identified that shed capsule components of AB99 bound with 8E3 formed soluble immune complexes and demonstrated *in vitro* adherence to human lung epithelial cells, thereby positing (i) these immune complexes at high concentrations acts as a “binding sink” for immune

molecules, overall depressing the activity of phagocytic cells, or (ii) 8E3-A. *baumannii* complexes enhance infection through increased adherence to and invasion of host cells by interacting with Fc receptors. The authors of this study do acknowledge that intrinsic properties of the capsule and virulence factors could also contribute to the observed ADE of infection in mice. Thus, future studies could also investigate if and to what degree any specific chemistries of cell surface structures (i.e., CPS, LPS, or LOS) or virulence factors play a role in the overall context of antibody-mediated enhancement of bacterial infection.

ANTIBODY-MEDIATED INHIBITION OF PHAGOCYTOSIS

One of the functions of antibodies is to opsonize bacteria, allowing recognition by Fc receptors and leading to increased phagocytosis. Paradoxically, specific antibodies that inhibit phagocytosis of *P. aeruginosa* have been described. Serum from patients with CF were found to inhibit phagocytosis by both normal and CF alveolar macrophages, in contrast to NHS, which promoted phagocytosis (129, 130). IgG specific for *P. aeruginosa* LPS was found to correlate with phagocytic inhibition (131) and, when purified, was found to inhibit both the rate and absolute bacterial uptake by alveolar macrophages (132). Cats infected with O-antigen-expressing *P. aeruginosa* also developed strain-specific phagocytic-inhibitory serum over time (85). If these LPS antibodies are primarily IgG2 as previously found (23), it may be that as IgG2 has no or low affinity for many of the Fc receptors expressed by macrophages (133), the antibody-coated bacteria are masked from targeted killing. As Ig proteases have also been shown to prevent opsonophagocytosis, it may be that *P. aeruginosa* proteases such as LasB are also required for this mechanism to occur.

TREATMENT OF BACTERIAL ADE

In only a few reported cases of bacterial ADE has any targeted treatment of the specific antibody been attempted. "Cloaking antibodies" in *P. aeruginosa* infection have been shown to correlate with worse lung function (23). Two patients identified in the initial study with cloaking antibodies had severely impaired lung function, multidrug-resistant *P. aeruginosa*, and had exhausted all standard treatment options (71). Removal of the IgG antibody had been shown *in vitro* to restore bactericidal activity of the serum against these strains (23). Thus, the use of plasmapheresis as a novel treatment to remove cloaking antibody, restore normal immune killing, and ameliorate infection was proposed. Each patient was given plasmapheresis followed by intravenous pooled immunoglobulin (IVIg). After treatment, both patients were able to return home; their sputum was *P. aeruginosa* negative and a sustained decrease in the inflammatory marker C-reactive protein was observed. Cloaking antibody titers dropped significantly with plasmapheresis but increased over 90 days, such that these sera were unable to kill their cognate *P. aeruginosa*. Reemergence of inhibition correlated with the reappearance of *P. aeruginosa* in sputa, increased symptomatology, and poorer responses to subsequent antibiotic courses. This prompted a second round of plasmapheresis for one of the patients, resulting in a similar improvement in patient health.

In a more recent case, a similar treatment was again used where a patient with CF had developed *P. aeruginosa* infection post-lung transplant, which continued to spread despite aggressive incision and drainage and treatment with two different antibiotic cocktails (134). Posttreatment, the patient recovered, with no further infective complications and vastly improved allograft function. As all patient isolates displayed resistance to antibiotics used routinely for respiratory infections, this treatment offers an exciting and novel method to treat multidrug-resistant bacterial infections.

CONCLUSION

Despite a focus on viral ADE in recent years, ADE has been shown for multiple bacterial infections in both animal models and human cohorts. The mechanisms underlying this enhancement are distinct from those found in viral diseases, ranging from

mediating serum resistance, protecting against phagocytosis, and increasing bacterial virulence functions. These antibody-mediated mechanisms are found in a wide array of diseases and bacterial species, indicating that ADE of bacterial infection may be more prevalent than expected. As in viral ADE, whether the specific antibody is protective or deleterious depends on many elements, including the expression of various virulence factors of the bacteria, site of infection, and titer of the antibody. Continuing efforts to develop safe and effective vaccines for various bacterial infections should include awareness of the possibility of bacterial ADE in certain cases, which may even explain some vaccination failures in the past. Finally, treatment of bacterial ADE by removal of the cloaking antibody has been successfully demonstrated and may be a viable alternative treatment option for otherwise drug-resistant bacteria.

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