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ARTICLE

# The complement system: an overview of deficiency states and associated diseases

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**ABSTRACT**
The complement system is an integral component of innate immunity, comprising over thirty key free and membrane-bound proteins. Complement molecules play effector roles—either opsonizing target cells for macrophages or directly neutralizing targets themselves—by utilizing three cascading pathways: the classical pathway, lectin pathway, and alternative pathway. All three pathways sequentially generate molecules in a particular order, and converge in the terminal pathway to form a membrane attack complex. The formation of a membrane attack complex facilitates the lysis of an invading bacterium. A number of complement receptors act to mediate the biological function of the system—receptors also permit the enhancement of antigen–antibody efficacy in responding to invading microbes. Extreme regulation of the complement system maintains a responsible concentration of complement proteins and helps to prevent malefic issues that can cause autoimmunity. Deficiencies in complement proteins generally creates immunodeficiencies, and are often caused via environmentally-acquired or hereditary traits. Complement deficiency can lead to disorders such as lupus, as well as allow recurrent infection of bacteria such as in the case of meningitis. Therapeutic remedies are relatively ineffectual in treating complement deficiency, and most operate only by circumventing the need for complement proteins. New research for complement-deficient therapies have yielded mixed results—meanwhile many individual cases of deficiency are left undiagnosed.

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## Introduction†

The complement cascade is an important system that plays a role in both the innate and adaptive immune systems. This system enhances the ability of antibodies to clear microbes and infected cells from an organism through selected pathways. There are three different pathways the complement system carries, including the *classical*, *lectin*, and *alternative pathways*.[5]

Many proteins are included in the function of this system, which are mainly synthesized in the liver, and are then distributed among the body tissues and fluids. The plasma proteins that are mostly involved in the system are B, C1-C9, and D. They are mainly enzyme precursors that initiate enzymatic reactions that make up the complement system's final products. Distinct activators activate the pathways but then all follow common complement components. All activated pathways follow into the cleavage of complement component C3. This cleavage forms C3b, which acts as an opsonin and a small fragment, C3a, which promotes inflammation. Once C3b binds to a pathogens surface, complement protein C5 forms C5b and C5a. C5a attracts macrophages and activates mast cells while C5b unites with C6, C7, C8, and C9 to form a complex known as the membrane attack complex (MAC). When MAC is bound to a pathogens membrane, it can con-

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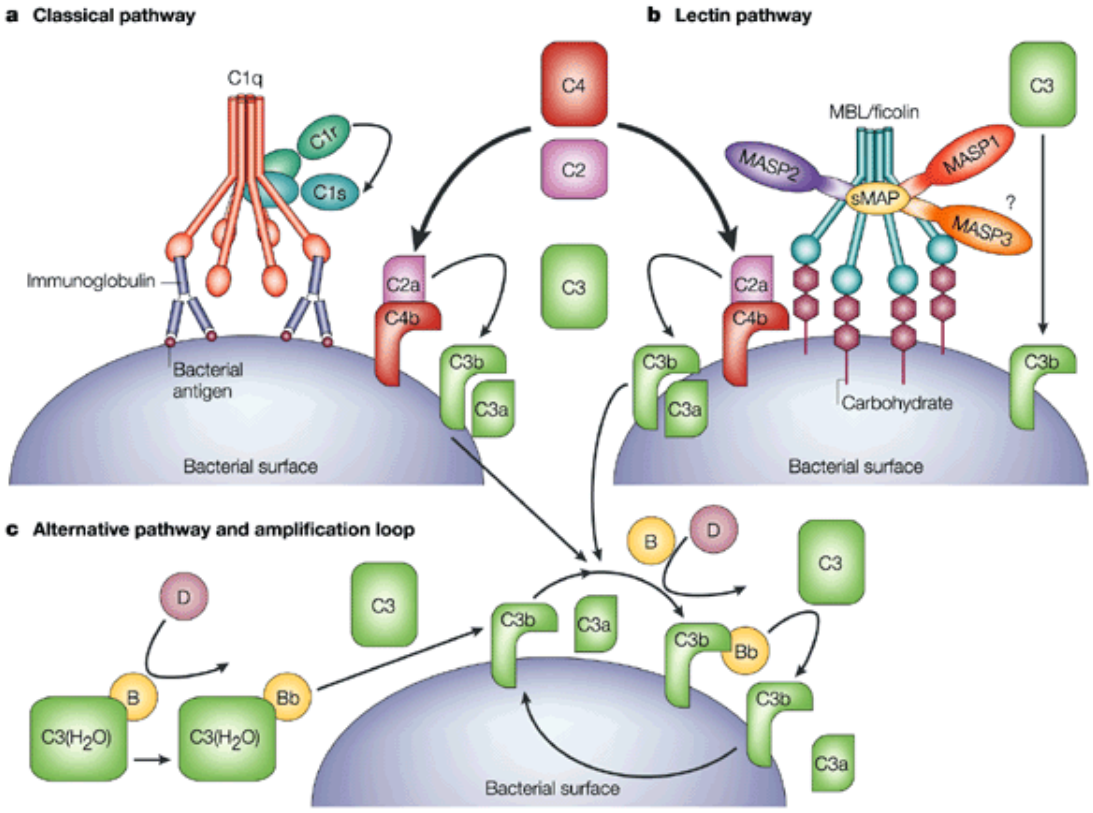


**Figure 1: Three known pathways for complement cascade.** (**a**) Classical pathway is initiated by antigen–antibody (Ag–Ab) interactions with IgG and IgM isotypes. C3 convertase is generated to cleave its respective protein and target the invading cell. (**b**) Lectin pathway is initiated by the formation of bonds, notably by mannose-binding lectin. The structure is similar to the classical pathway, except antibodies bound to the target cell are not recognized. (**c**) Alternative pathway is activated by the direct binding of C3b on a microbial surface. In all pathways, the formation of C5 convertase triggers the terminal complement pathway to form a membrane attack complex (MAC).

tribute to the cells death through lysis.[7]

The end of each pathway results in three major activities: the production of opsonins by making the pathogen more susceptible to phagocytosis, the induction of inflammation, and the killing of the pathogen. All of these steps play a crucial role in the removal of foreign microorganisms by the immune system.[3]

## Variable Pathways†,‡

The complement system has three known cascading pathways that converge onto single points of execution. These pathways are depicted in Figure 1. All pathways converge after the generation of C5 convertase. The production of this enzyme initiates the terminal pathway, leading to the formation of MAC.

### Classical Pathway†

The main activator for the *classical pathway* is the interaction between antigen and antibody, also known as the antigen-antibody complex. Other activators include soluble antigen-antibody complexes, viruses, necrotic cells, and subcellular membranes.

This reaction then leads to the activation of complement component C1. C1 contains three different proteins: C1q, C1r, C1s. C1q proceeds to bind to the Fc region of two IgG molecules or one IgM molecule bound to an antigen. C1s cleaves C4 into C4a and C4b and proceeds by also cleaving C2 into C2a and C2b. C2a then combines with C4b of the cell's surface to create the classical pathway C3 convertase. The C3 convertase proceeds to activate the C3 protein complex.

### Lectin Pathway†

The *lectin pathway* is identical to the classical pathway, having the same steps when generating the complement components. The only difference is that in order to activate the lectin pathway, mannose-binding lectin (MBL) must bind to mannose containing carbohydrates. Mannose residues are present in bacteria, fungi, and yeast particles. MLB circulates in the plasma as a complex with two proteases known as the mannose-associated serine proteases, MASP-1 and

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MASP-2. MASP-2 acts as a convertase, cleaving C4 and C2 to form C4b2a on the surface of the bacterium. As in the classical pathway, C4b2a creates the C3 convertase.

In some individuals, there can be a mannose-binding lectin deficiency. This condition causes low levels of the protein MLB in the blood, causing affect in the immune system. These individuals have a higher increased risk of infections in their body systems. Children that have been affected with MLB deficiency have a higher risk of infection and meningococcal disease.

This meningitis disease is a serious bacterial infection causing the membranes that cover the brain and spinal cord to become inflamed. MLB deficiency in adults increases the risk of viral infection, pneumonia, and meningococcal disease.

## Alternative Pathway‡

The *alternative pathway* is initiated by the presence of foreign cell surfaces on pathogenic organisms and occurs in the absence of an antibody. The activators of this pathway include cell walls of yeast, lipopolysaccharide (endotoxin) in the outer membrane of gram negative bacteria, and teichoic acid found in the cell wall of gram positive bacteria. In contrast to classical and lectin pathway which requires protein-protein or protein-carbohydrate interactions, the alternative pathway is capable of autoactivation. The pathway begins with the serum protein C3 which spontaneously undergoes hydrolysis to form C3a and C3b, C3b being the product which binds to proteins and carbohydrates expressed on cell surfaces of pathogens. Surface-bound C3b binds circulating factor B, which is cleaved by Factor D to produce the alternative pathway C3 convertase, C3bBb.

The membrane-bound C3 convertase is unstable in nature and has a low half-life but its activity is prolonged when it binds to the serum protein Factor P. With greater stability, the enzyme is now able to play a role in the amplification loop and continues to cleave C3 and produce C3b. Incorporation of the C3b protein with any C3 convertase of the complement pathways results in the formation of the C5 convertase. C5 converstase cleaves C5 to generate C5a and C5b, which stays bound to the membrane and the cascade continues until the membrane attack complex (C5b-C9) is formed. The complex generates a transmembrane channel in the cell membrane and eventually leads to cell death due to membrane disruption and influx of ions and water into the cell. C3a and C5a which were produced earlier in the reaction are involved with inducing inflammatory responses.[23]

## Receptors and Regulation‡

There are many complement receptors that are expressed on various cell types and are involved in carrying out many of the biologic functions of the complement system. The interaction between receptors

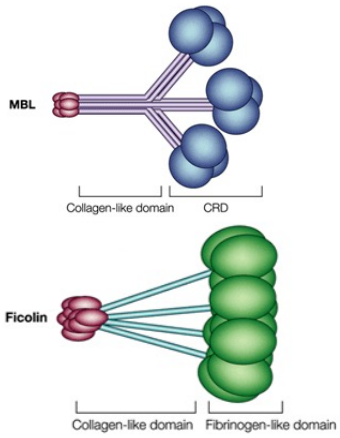


**Figure 3: Mannose-binding lectin (top) and ficolin (bottom) initiate the lectin pathway.**

found on immune and non-immune cells with complement proteins mediate numerous functions such as phagocytosis, inflammatory response, and localization of immune cells. Complement proteins C3b and C3bi coated on microorganisms enhances pathogen uptake via phagocytosis by cells such as macrophages and neutrophils that express the appropriate receptor. Proteins C3a, C4a, and C5a are involved in activation of inflammation and chemotaxis of leukocytes. The receptors for these molecules are expressed on cells such as smooth muscle, endothelial cell, macrophages, monocytes, neutrophils, and eosinophils. All three of these proteins facilitate smooth muscle contraction, histamine release from mast cells, and increase vascular permeability.[2] C5a, for example, is a chemoattractant and the receptor for this protein is expressed on neutrophils and monocytes. Activation by C5a causes these cells to migrate to the source of inflammation and eliminate the pathogen.[6] Although these receptors help mediate the elimination of the pathogen, they can also be used by some viruses to promote infection.

HIV can cause HIV-associated neurodegenerative disorder (HAND), a form of neural damage caused by HIV replication and immune activation in the brain. When HIV invades and replicates in normal host cell, it incorporates complement regulators in the viral envelope from the host cell in the budding process. As a result, C3 proteins can accumulate on the surface of the virus but are resistant to lysis due to the presence of the regulator proteins. Now, the virus can utilize the complement receptors found on monocytes and lymphocytes and can use these cells as carriers to cross the blood-brain-barrier to enter the brain.[22] After crossing the BBB, HIV-infected monocytes become macrophages and begin to replicate the virus and express neurotoxic molecules which further activates other cells. All of this leads to neuronal damage since it induces the production of complement proteins and neurons express very low levels of complement inhibitors. Therefore, the patient can suffer from conditions such as depression, anxiety, and HIV-associated dementia. However, the exact pathogenesis of HAND due to neuronal loss and injury remains unclear.[9]

The complement system is highly regulated and

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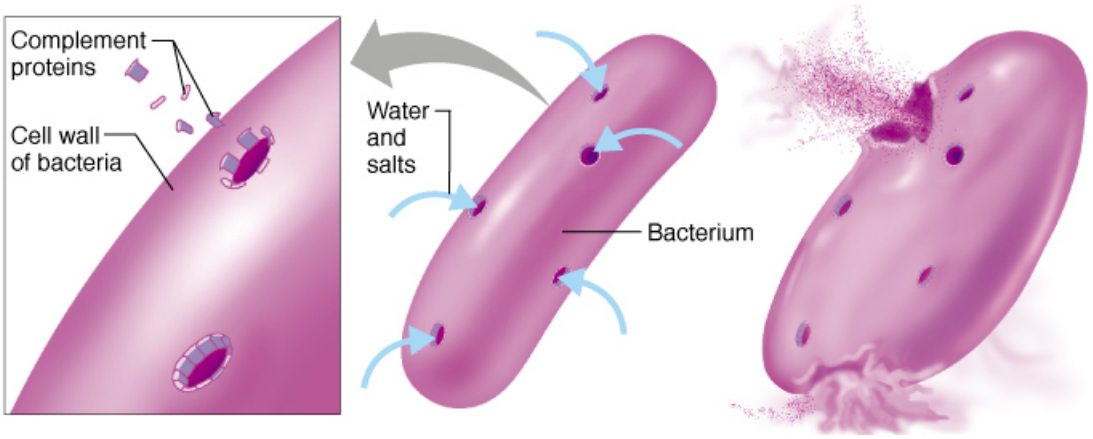


**Figure 2: Complement-mediated lysis of foreign bacterium.** Complement molecules that have been activated in response to a foreign invader form lattice structures which puncture the membrane wall of the invading cell. The punctured holes then allow water and other fluid salts to flow into the bacterium. The cell swells from the influx of material and eventually lyses.

without control, results in inappropriate activation on normal host cells and auto-inflammatory condition—for example, C3b is also able to bind to host cell. The regulator proteins are present in the serum as well on the surface of normal host cells. Such molecules are not present on microbial cells and therefore, the complement pathway proceeds to kill the pathogen.[2] Although, there are pathogens that have evolved mechanisms to evade this. The importance of such regulators is evident in patients experiencing a number of infectious and inflammatory conditions.

An important molecule controlling the complement system is factor H, which is a soluble glycoprotein mainly secreted by the liver and present in serum. Factor H controls the complement activation in several ways: it binds to host cells and protects them against C3b deposition; it reduces the formation of the alternative pathway C3 convertase; and promotes the factor I-dependent degeneration of C3b. Mutations in the factor H gene are associated with many problems including kidney disease and can lead to recurrent bacterial infections. The increased tendency for bacterial infection is observed because with the absence of factor H, the C3 convertase activity is sustained and depletes complement component C3 in the circulation, leaving the host susceptible to subsequent invasion by pathogens.[16]

Kidney disease is also seen in patients that have a defect in complement factor H. As mentioned earlier, this results in continuous activation of the alternative pathway and the continuous formation of the C3 convertase. The glomerular basement membrane of the glomerulus lacks membrane-anchored complement regulators and relies on factor H for its protection. As a consequence, this leads to continuous C3 deposition and thickening of the membrane and ultimately, impairs renal filtration and function.[11]

## Deficiency States§

To reiterate, the activation of the complement system plays an important role for one to prevent infections, but something else that can come with the territory are autoimmune diseases. One for say triggers inflammatory response by immune complex deposition in tissue. Deficiencies in the early components in the classical pathway (C1q, C1r, C1s, C4, C2), has an association with the progression of Systemic Lupus Erythematosus (SLE).

### An Overview of Lupus§

Ideally, during normal apoptosis cells would release all the inner substance as well as its DNA, and all the components would be phagocytized to prevent damage to host. Systemic lupus erythematous (SLE) is clinical heterogenous disease with an autoimmune origin. Characterized by inflammation and auto-antibodies are produced against their cell nuclear components such as DNA and histones known as antinuclear antibodies (ANA) as well as ribonucleoprotein.[13] Those with certain susceptibility genes would have a deficiency in the classical pathway complement protein C1q, C4, and C2.

In addition to environmental impacts as UV-rays to damaging a cell's DNA and triggering apoptosis, the deficiencies would reduce the clearance of the apoptotic cells and their DNA would be released. This continual exposure to self-DNA would cause it to be recognized as foreign substance, which anti-DNA antibodies are produced that will target DNA specifically. The antigen-antibody complexes of anti-DNA will circulate and begin to target everything in the body that has DNA, giving the name "systemic". The deposition of

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immune complexes in organs as the skin, kidney, and joints, causes inflammation as well as tissue damage is known as a Type 3 Hypersensitivity reaction.[13]

## C4 and B-cell negative selection, and APC§

SLE is a B-cell dependent autoimmune disease with the production of antibodies for nuclear antigen as dsDNA and histones.[1] The tolerance hypothesis proposes that complement and natural immunity act in accordance to localize lupus-antigens to sites within the lymphoid compartments where developing B cells undergo negative selection. There is a study that examines the role of C4 and how it plays a role in self-reacting B-cells. Deficient mice were bred with rearranged Ig heavy chain and anti-chromatic transgenes specific for chromatin. Those mice's that had normal or sufficient C4, self-reactive transgene B cells are halt from maturing at the immature stage of development and go through apoptosis, a role process known as negative selection. In comparison to those that has a absence or deficiency of C4, B-cells that were self-reactive continued to mature and secret self-reactive antibody of IgM and IgG. These results agree with the Tolerance hypothesis in which, seeing that importance role of C4 in the regulation of self-reacting B-cells.

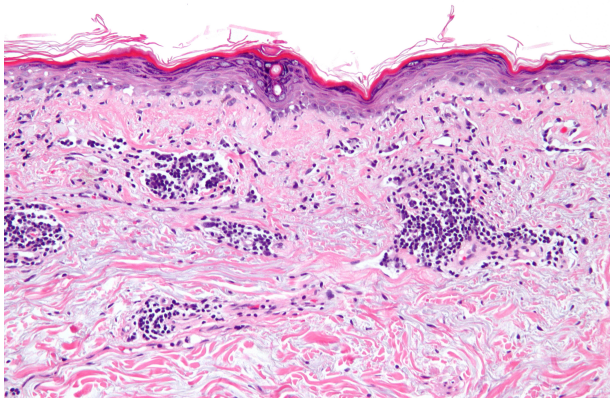

**Figure 4: Micrograph of vacuolar interface dermatitis as observed in a lupus case.**

In addition, environmental impacts as UV-rays to damaging a cell's DNA and triggering apoptosis. Blebs would form and bulge off the cell, spilling out nuclear components, but deficiencies in the classical pathway components, as C1q, would reduce the clearance of the apoptotic cells and self-DNA. This continual exposure to self-DNA would cause it to be recognized by self-reacting B-cells, which anti-DNA antibodies (ANA), or in general terms immune complexes are produced that will target self-DNA specifically. Dendritic Cells have Toll-like receptors that bind to these immune complexes that too can recognize self-nucleosome (DNA + histones). This interaction will cause the release of cytokines for inflammation as IL-12, IL-6, IL-10, IL-17, TNF-a., as well as other cytokines for T-cells and macrophage recruitment. These will be presented to T-cells, that will interact with B-cells for maturation for antibody production against self-components. The antigen-antibody complexes of anti-DNA will circulate and begin to target everything in the body that has DNA, giving the name *systemic*. The deposition of immune complexes in organs as the skin, kidney, and joints, causes inflammation as well as tissue damage is known as a Type 3 Hypersensitivity reaction.[13]

## SLE Conditions and Diagnostics§

The most common manifestations include fever, rash, arthritis/joint-pain, fatigue. Those that have an acute chronic inflammation of lupus are susceptible to infections and cardiovascular diseases. The more severe end of the spectrum, SLE can cause nephritis, neurological problems, anemia (having few red blood or hemoglobin than normal) and thrombocytopenia (decrease in the number of platelets in blood) emphasizing that SLE can appear in many places as musculoskeletal, dermatological, and cardiac among many things.[13]

The Systemic Lupus International Collaborating Clinics (SLICC) group developed a new set of classification criteria in 2012, which at least 4 criteria must be met, at least on from clinical and at least one from immunological, for an individual to be classified with SLE. These are going to deal with the clinical criteria, and the 1st deal with the skin and the sun exposed area called the Malar rash, known as the butterfly rash, having fixed erythema over the malar eminences which spare the nasolabial folds, is diagnosis as Acute cutaneous lupus. 2nd is a Discoid rash is diagnosis as Chronic cutaneous lupus, which are plaque like erythematosus raised patches that can scar from sun exposure.[14] 3rd is Oral ulcers on palate, buccal mucosa, gingiva, and or nose. 4th is non-scarring alopecia, hair loss on the scalp, face or other areas of the body. The 5th is Synovitis, inflamed synovial membrane, known as arthritis involving two or more joints, characterized by swelling or effusion or tenderness in 2 or more joints and 30 min or more of morning stiffness.[13] The 6th is deal with Serositis, through inflamed outer membrane tissue. This can manifest into pleuritis, inflammation around the lungs and chest cavity, causing pleuritic pain, pleural rub, pleural effusion and Pericarditis, inflammation of the lining of the heart, leading to ECG changes, rub, pericardial effusion.[14] The 7th are renal disorders as abnormal amounts of protein in urine known as Proteinuria (>3.5g/day). An example is albumin leaving the blood and being a part of the urine. This would cause individual to get hypoalbuminemia. As well cellular casts as blood in urine, these being apart of the nephrotic syndrome and nephritic syndrome. The 8th deals with the brain and

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neurological symptoms as seizures and psychosis. The 9th deal with the blood that causes Hematological disorders. Hemolytic anemia would be caused is blood cells are targeted, thrombocytopenia if platelets are targeted, Leukopenia if white blood cells are targeted, or Lymphopenia is lymphocytes are targeted. What is to be noted that the immune system can attack itself.[14]

The last criteria fall under Immunological criteria and the first deal with anti-nuclear antibody (ANA), which an ANA test and ANA levels are above laboratory reference range. The next are antibodies that doesn't bind to nuclear as A) Anti-Sm (Anti-smith), being antibodies that target ribonuclear proteins, B) Anti-dsDNA antibodies, and C) Anti-phospholipid antibodies, which are usually targets proteins bound to phospholipids. Anti-phospholipid has three types anticardiolipin, lupus anticoagulant (lupus antibody, and anti B2 glycoprotein 1. The last two are low complement C3, C4, or CH50, and a Direct Coombs test (in absence of hemolytic anemia). Not a part of the criteria is that further diagnosis can be through medical specialist. As biopsy of skin, kidney, and muscle, as well as MRI of muscle and heart to give a few. The three most common diagnosis are Hematologic RBC count, ANA test (+), and Renal test for urine analysis.

### Etiology and Epidemiology§

SLE is due to three etiological factors: genetics, environment, and immunological. Those that inherited genes made them susceptible to the disorder. Things as impaired clearance of immune complexes and apoptotic bodies. Environmental factors as UV light, viruses such as Epstein-Barr virus (EBV), drugs like hydralazine, procainamide, and penicillamine, as well as sex hormones (estrogen) can trigger the disorder by inducing apoptosis of healthy cell. The most significant immunological abrasion is through defective elimination of self-reacting B-cells and T-cells. They recognize self-antigen and attack self-cells, tissues, and organs.

SLE can affect individuals of all ages and ethnic groups, as well as both sexes. Approximately 90% of patients with SLE are women of child bearing age, and are observed highest in incidence in African American, which estrogen plays a role in SLE which may explain why female are more likely to have SLE than male. The incidence range of SLE is from 1–10 per 100,000 individuals a year and prevalence are 20–70 per 100, 000 individuals per year.

### SLE Treatments§

Adjunct treatment purpose is to assist in primary treatment. One form or treatment is avoiding sunlight or UV protection and vitamin D supplements, which doesn't cure SLE, but relieves the symptoms. Things as low dose of aspirin, calcium, bisphosphonates, statins, and blood pressure drugs should be considered.[8] Those that smoke, take medication that is known to trigger SLE (as hydralazine and TNF-alpha antagonists) have exposure to sunlight will worsen their conditions. Wearing long clothing, using sun blocker protection lotion and sprays with UV-A/UV-B filters (SPF 50+) being applied 30 before UV exposure, or spending more times in doors are recommendation for protection.

Topical treatment Glucocorticoid Class IV as Clobetasolt can be applied to the scalp, palms, and soles, whereas in other areas only class II (e.g., methylprednisolone aceponate) and class III (e.g., mometasone furoate) glucocorticoids are recommended. Due to the adverse effects (e.g., atrophy, teleangiectasia, perioral dermatitis) glucocorticoids should be administered only intermittently and not long term, particularly not for butterfly rash. Long term treatment without the risk are the use of topical calcinerium inhibitors (tacrolimus ointment [level of evidence I], pimecrolimus cream [level of evidence II]).[8]

Immune suppressor drugs as azathioprine, methotrexate (have been known to be effective on joints and skin lesion), or mycophenolate mofetil non-steroidal in addition to anti-inflammatory drugs (NSAIDs), and hydroxychloroquine, which is used in malaria treatment but has been found to help those with SLE.

Researchers studied the role of the female hormone estrogen, also known as 17β-estradiol, in the immune system in systemic lupus erythematosus (SLE). It had a negative role in which through studies conducted in both animal models and humans have proposed that estrogen enhanced SLE severity and the occurrence of flares by promoting inflammation, increase the expression of autoantibodies and enhance reactivity to exogenous antigens as well as induce activation of interferon-stimulated genes. There has been some that say that the X chromosome play a role in inducing SLE, which those that are XXY are more susceptible to SLE disorder, but this is still very uncertain and is being researched on. A prevention is not taking birth control, which it contains estrogen, in addition to progestin.

## Simplified Pneumonia*

Pneumonia is an inflammatory lung condition caused by *Streptococcus pneumoniae*. The bacteria is detected when a macrophage recognizes a foreign pathogen and performs phagocytosis thereby releasing cytokines, which recruit other macrophages. These macrophages will make way to the blood stream as APC and will adhere to lymphocytes. Lymphocyte T cells bind to APC releasing interferon attracting lymphocyte B cells. B cells will create antibodies that will travel down the bloodstream until they reach the infected site. These antibodies will

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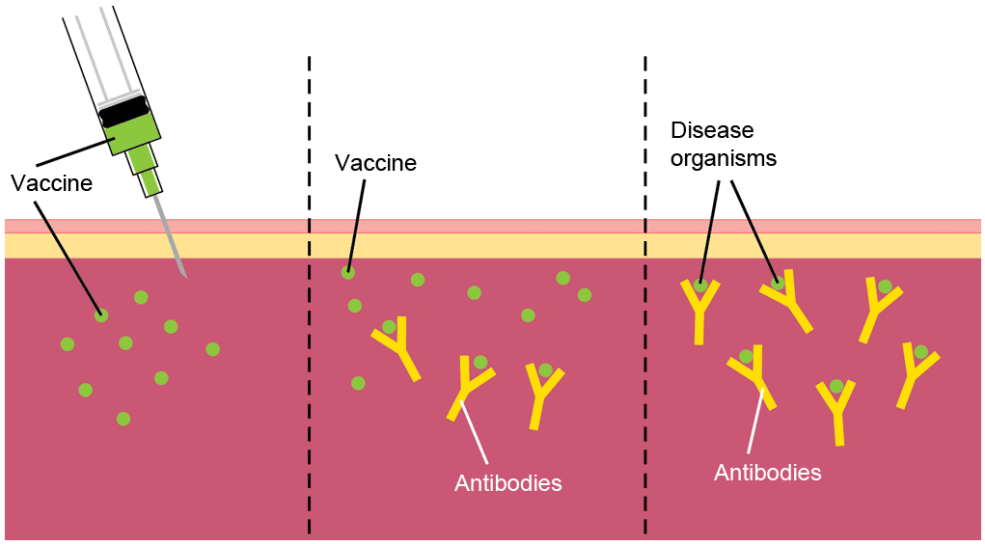


**Figure 5: Basic vaccination mechanism for antibody stimulation.** Weakened causative agents are injected into the host, promoting antibody production in response. The proliferated antibodies remain in the serum after clearing the vaccine agents, and can then rapidly respond in the event that the host is infected by more hostile forms of the disease.

adhere to the bacteria causing it to stop reproducing or so macrophage can engulf it. The bacteria is able to bypass innate immunity due to the creation of some proteases, they will cleave IgA and IgG and produce factors that degrade CTB or inactivate c3v. Symptoms include fever, chills, cough, rapid breathing, difficulty breathing, and chest pain.

Capsule layer plays a major role in *Streptococcus pneumoniae* infection by blocking the phagocytic cells. The capsule layer is made up of polysaccharides interfering with phagocytosis by blocking CCB and phagocytic receptors. Pilli helps with the colonization of the upper respiratory tract. Increases amounts of TNF during invasive infection.

To defend itself against *S. pneumoniae*, the body uses intracellular killing (block) where pneumonias adheres to the mucus layer which tries to destroy the bacteria by engulfing or degrading it by lysosome fusion. This is known as a normal approach.

The body may also utilize antibacterial peptides and proteins or inflammatory response. In the former, if bacteria passes through the mucus layer inside the cell and reaches the extracellular matrix antimicrobial agents will start producing. The antimicrobial proteins will start degrading bacteria to control their growth and division.

If that fails we move on to the third defense mechanism. Bacteria reaches the epithelial cell through the basal layer. when it reaches the bloodstream they will need to use normal immune system cells to prevent further damage. At this point the inflammatory response kicked in and will call upon chemical mediators and neutrophils, basophils, and other molecules to regulate the growth therefore causing inflammation.

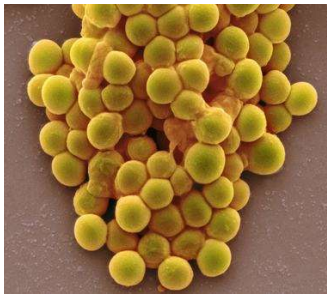

**Figure 6: Scanning electron micrograph of microbial *Streptococcus pneumoniae*.**

Finally, if this system fails to check growth and development of bacteria then the innate immunity comes to play. The complement system will play the important role in the CCB protein. Yet if this system fails, the bacteria will spread.

Treatments for pneumonia include MDR stain (penicillin, amoxicillin, or macrolides) and vaccines. Anti-pneumococcal vaccines are based on various capsular (polysaccharides) antigens derived from highly prevalent strains.

## Therapeutic Remedies¶

Due to the ubiquitous nature of the complement system, any disorder therein is generally difficult to diagnose. It is estimated that over ninety percent of all patients with complement deficiency states are never recorded.[21]

Because of the rarity of diagnosed complement deficiencies, there exist only limited options of therapeutic treatment—some of which are still considered to have dubious results. In general, most of the effective treatments work by circumventing the issue at hand rather than curing the deficiency itself. Indeed, immunotherapies for complement deficiency vary widely and depend almost exclusively on the threatening disease present.

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Vaccination, for example, is often considered to be a viable treatment for individuals with complement deficiency.[17] Immunizations are intended as a supplementary aid to those with deficient complement systems. While not directly treating the deficiency, vaccines provide a supportive role by promoting more effective antibody proliferation—a critically important feature for those who have low levels of complement molecules.

### Deficiency-associated Meningitis¶

*Meningitis* is a collective term that designates the hyperinflammation of neural membranes known as meninges.[20] Meningitis can be caused by a host of different pathogens including bacteria, viruses, and fungi. Bacterial infections are caused by *Neisseria meningitidis* and are conventionally neutralized by the complement system, either through the lectin or alternative pathways.

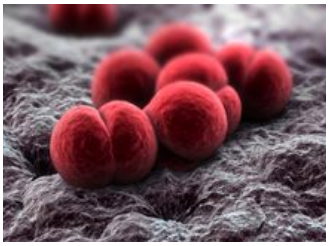

**Figure 7: Scanning electron micrograph of microbial *Neisseria meningitidis*.**

Individuals with deficiency in the terminal complement pathways—including C5, C6, C7, C8, and C9—are increasingly susceptible to recurrent infection by *N. meningitidis*.[10] The complement system has a well-documented role in neutralizing meningococcal diseases, especially those precipitated by microbes. Thus, an impaired complement pathway is a significant risk factor for meningitis. To counter this, routine immunization with meningococcal vaccines must be administered to these compromised individuals at a much higher rate than the general population.

For the general public, a meningococcal vaccine operates by promoting proliferation of antibodies for complement-mediated bactericide and opsonization of phagocytes. In deficient patients, increased dosage frequencies stimulate the production of antibodies and phagocytic abilities in lieu of, or despite weakened, complement cascade enhancement.[15]

### Antibiotic Therapy¶

Specialized antibiotics are another prescribed method for aiding individuals with compromised complement systems. *Streptococcus pneumoniae*, the causative agent of pneumonia, has recently evolved alarmingly high-levels of resistance against conventional antibiotics. This is of great concern to complement deficient individuals, who are much more vulnerable to the microbe. In such cases, third-generation cephalosporin antibiotics may be required to combat *S. pneumoniae*. It has been found that the antibiotic cefditoren greatly enhances complement-mediated phagocytic responses to *S. pneumoniae* infections.[18] Complement deficient individuals that receive these antibiotics appear to display immune responses to bacterial infection comparably on par with normal individuals.

## Concluding Remarks¶

As a component of human innate immunity, the complement system plays a crucial role in the body's fight against pathological invasions. Less than optimal functioning of the complement system—termed as *complement deficiency*—thus carries significant ramifications on the ability to fend off infection.

Complement deficient individuals usually suffer severely from disease effects that arise from their insufficient immune responses to microbes. Nevertheless, modern medical understanding of the complement deficient state is underwhelming, and most cases are never diagnosed. Current therapeutic methods for dealing with complement deficiency rely almost exclusively on combating the actual diseases, rather than treating the fundamental issue at hand.

There exists some interest in researching synthetic production of complement proteins as a method to combat complement deficiency. The injection of complement molecules grown *in vitro* to bolster deficient individuals has theoretical promise—however, most efforts are generally impossible in practice.[19] The extraction and isolation of suitable, healthy molecules from individuals who already have abnormally low numbers of them is a difficult procedure that makes cloning an even larger hurdle. Still, the development of complement therapeutics and drugs is spurred on by the ever-increasing knowledge of the system's role in combating certain diseases. By establishing the exact methods in which the complement system neutralizes targets, researchers hope to soon be able to replicate the mechanics in synthetics that can be used as an alternative for complement deficient individuals.

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We would like to acknowledge that this is not a real journal—and also that none of the material contained herein is based on any results from original research of our own.

### Conflicting Interests

The authors have declared that *many* exist. The authors have also declared that they refuse to disclose what these conflicts of interest are. Ethical science has shed a tear today.

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