Immunology

Lec.9

COMPLEMENT SYSTEM

By:- Dr.Mustafa Abdulhussein

COMPLEMENT SYSTEM

- **The complement system** is consists of more than 30 proteins that are either present as soluble proteins in the blood or are present as membrane-associated proteins that are important in defense against microbes. Many complement proteins are **proteolytic enzymes**, and complement activation involves the sequential activation of these enzymes, sometimes called an **enzymatic cascade**.

Pathways of Complement System :-

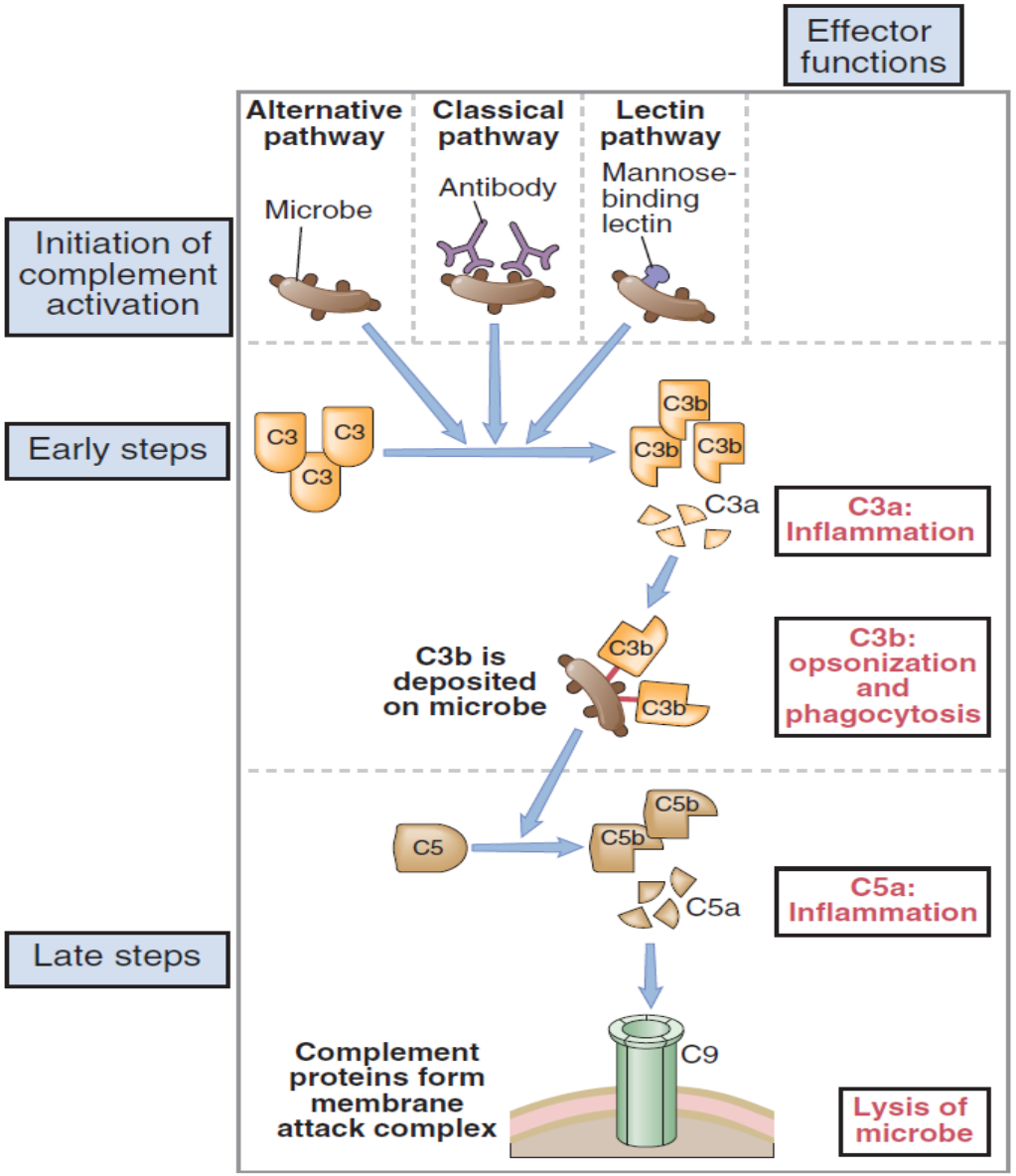

FIGURE 2-12 **Pathways of complement activation.** The activation of the complement system may be initiated by three distinct pathways, of which lead to the production of C3b (the early steps). C3b initiates the late steps of complement activation, culminating in the producti of numerous peptides and polymerized C9 (which forms the membrane attack complex, so called because it creates holes in plasma mei branes). The principal functions of proteins produced at different steps are shown. The activation, functions, and regulation of the compleme system are discussed in much more detail in Chapter 8.

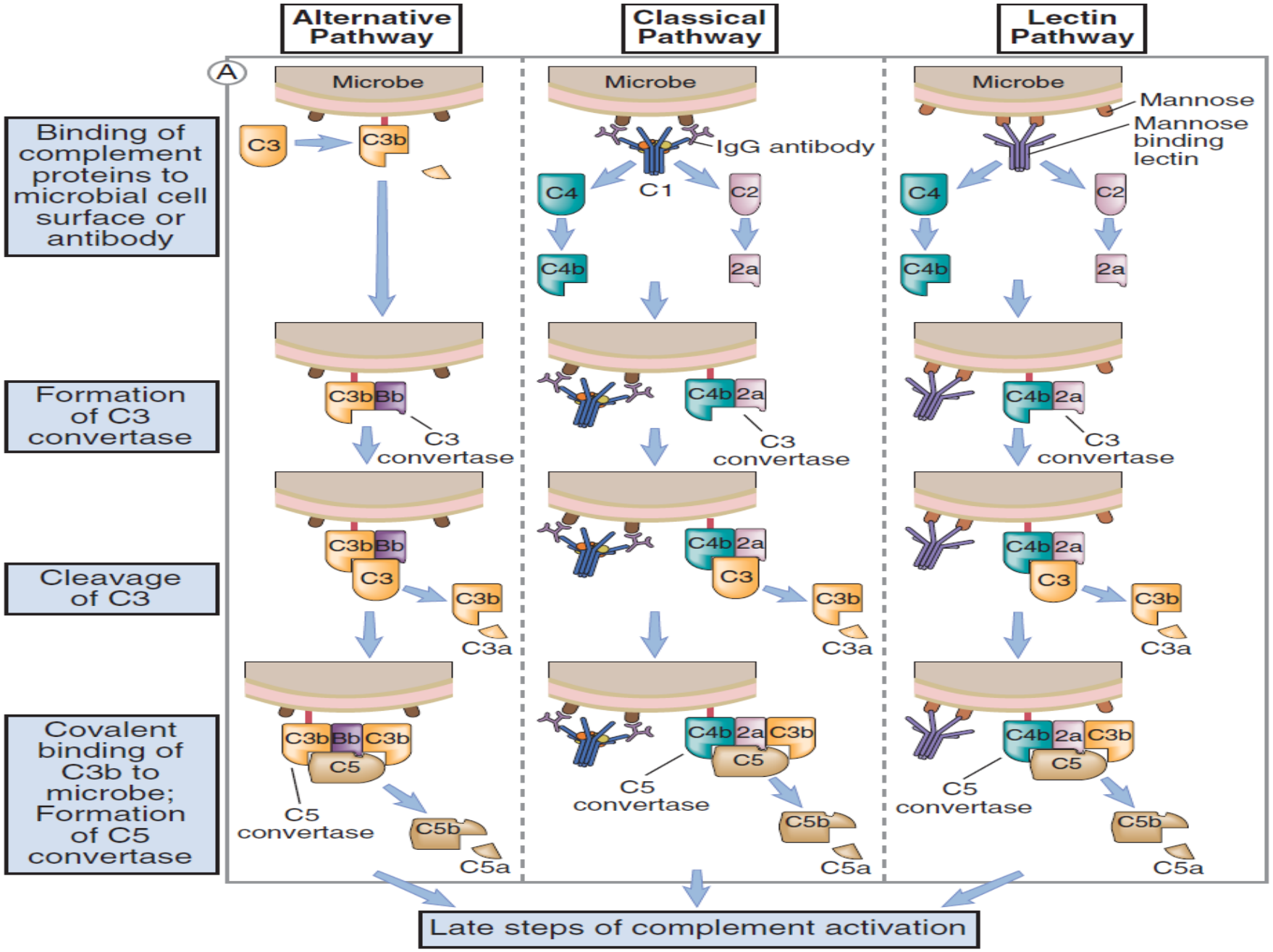

FIGURE 8-5 **The early steps of complement activation. A,** The steps in the activation of the alternative, classical, and lectin pathways are shown. Note that the sequence of events is similar in all three pathways, although they differ in their requirement for antibody and in the proteins used.

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Protein	Serum conc. (ug/mL)	Function
C3	1000-1200	C3b binds to the surface of a microbe where it functions as an opsonin and as a component of C3 and C5 convertases C3a stimulates inflammation
Factor B	200	Bb is a serine protease and the active enzyme of C3 and C5 convertases
Factor D	1-2	Plasma serine protease which cleaves Factor B when it is bound to C3b
Properdin	25	Stabilizes the C3 convertase (C3bBb) on microbial surfaces

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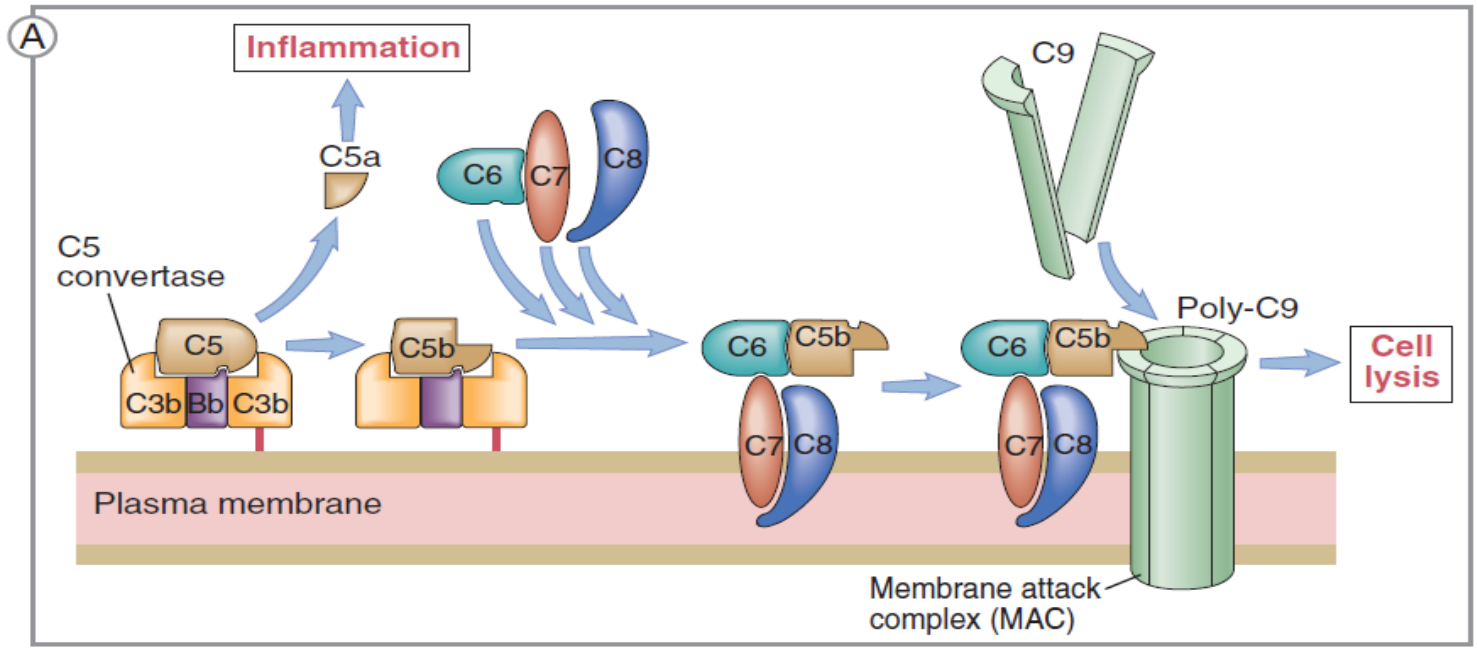
Protein	Serum conc. (ug/mL)	Function
C1 ($C1qr_2s_2$)		Initiates the classical pathway; C1q binds to Fc portion of antibody; C1r and C1s are proteases that lead to C4 and C2 activation
C4	300-600	C4b covalently binds to surface of microbe or cell where antibody is bound and complement is activated C4b binds to C2 for cleavage by C1s C4a stimulates inflammation
C2	20	C2a is a serine protease functioning as an active enzyme of C3 and C5 convertases
Mannose binding lectin (MBL)	0.8-1	Initiates the lectin pathway; MBL binds to terminal mannose residues of microbial carbohydrates. A MBL-associated protease activates C4 and C2, as in the classical pathway.

FIGURE 8-5, cont'd **B**, The important properties of the proteins involved in the early steps of the alternative pathway of complement activation are summarized. **C**, The important properties of the proteins involved in the early steps of the classical and lectin pathways are summarized. Note that C3, which is listed among the alternative pathway proteins (**B**), also is the central component of the classical and lectin pathways.



B

Protein	Serum conc. (μg/mL)	Function
C5	80	C5b initiates assembly of the MAC C5a stimulates inflammation
C6	45	Component of the MAC: binds to C5b and accepts C7
C7	90	Component of the MAC: binds C5b, 6 and inserts into lipid membranes
C8	60	Component of the MAC: binds C5b, 6, 7 and initiates binding and polymerization of C9
C9	60	Component of the MAC: binds C5b, 6, 7, 8 and polymerizes to form membrane pores

FIGURE 8-6 **The late steps of complement activation. A**, The late steps of complement activation start after the formation of the C5 convertase and are identical in the alternative and classical pathways. Products generated in the late steps induce inflammation (C5a) and cell lysis (the membrane attack complex [MAC]). **B**, The properties of the proteins of the late steps of complement activation are listed.

- **The complement system serves three functions in host defense:-**
- The complement system plays an important role in the elimination of microbes during innate and adaptive immune responses :-
- **First,** C3b coats microbes and promotes the binding of these microbes to phagocytes, by virtue of receptors for C3b that are expressed on the phagocytes.
- Thus, microbes that are **opsonized** with complement proteins are rapidly ingested and destroyed by phagocytes.
- **Second,** some proteolytic fragments of complement proteins, especially **C5a** and **C3a**, are chemoattractants for phagocytes, and they promote leukocyte recruitment (inflammation) at the site of complement activation.
- **Third,** complement activation culminates in the formation of a polymeric protein complex that inserts into the microbial cell membrane, disturbing the permeability barrier and causing either osmotic lysis or apoptotic death of the microbe.

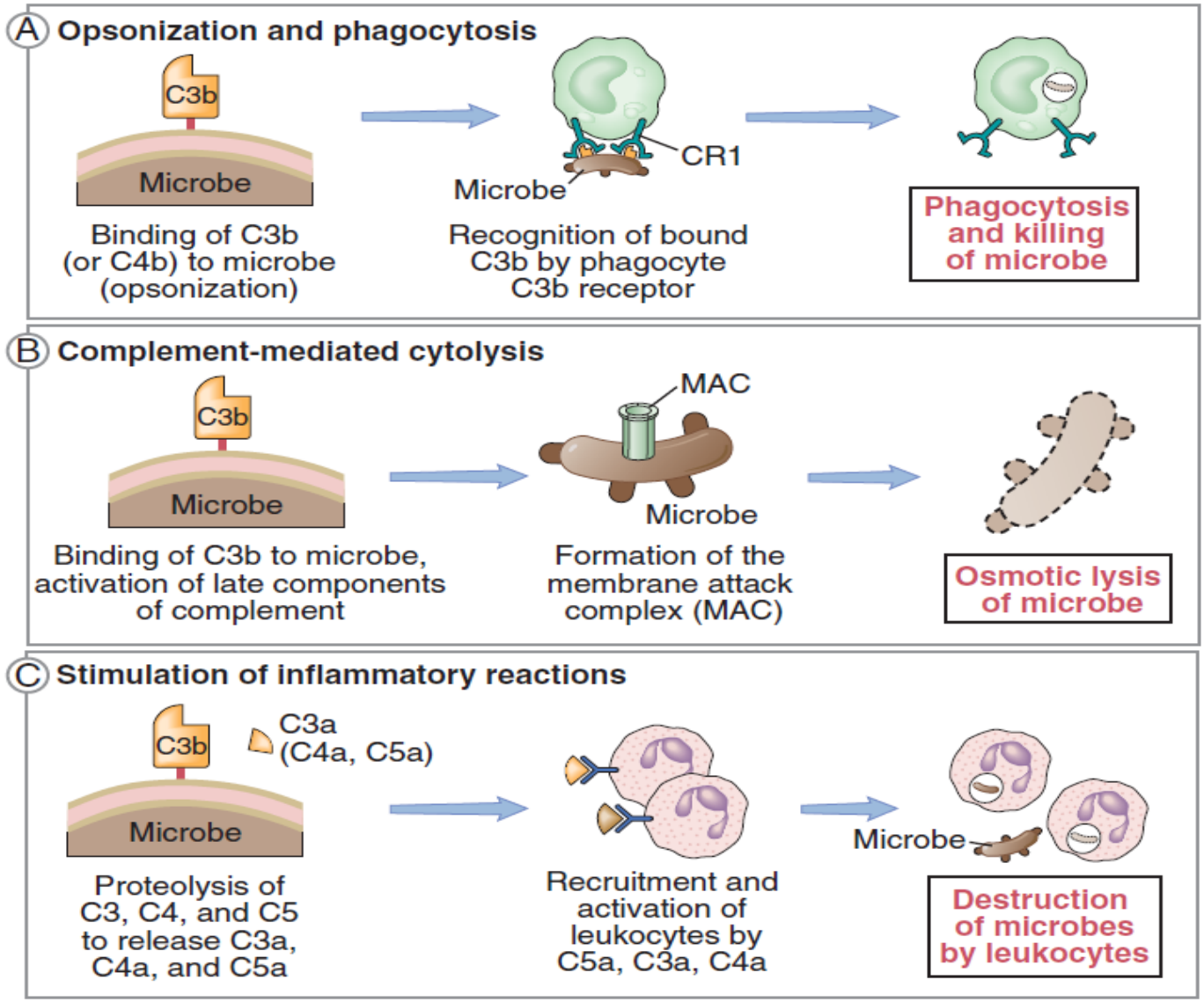


FIGURE 8-7 **The functions of complement. A,** C3b opsonizes microbes and is recognized by the type 1 complement receptor (CR1) of phagocytes, resulting in ingestion and intracellular killing of the opsonized microbes. Thus, C3b is an opsonin. CR1 also recognizes C4b, which may serve the same function. Other complement products, such as the inactivated form of C3b (iC3b), also bind to microbes and are recognized by other receptors on phagocytes (e.g., the type 3 complement receptor, a member of the integrin family of proteins). **B,** The membrane attack complex creates pores in cell membranes and induces osmotic lysis of the cells. **C,** Small peptides released during complement activation bind to receptors on neutrophils and stimulate inflammatory reactions. The peptides that serve this function are C5a, C3a, and C4a (in decreasing order of potency).

- **Defects in Human Complement Proteins :-**
- **1- Hemolytic Uremic Syndrome**

  Mutation of the factor H gene results in impaired C3 convertase activity and is associated with **atypical hemolytic uremic syndrome** (aHUS) wherein hemolytic anemia, thrombocytopenia and acute renal failure develop.
- **2- Systemic Lupus Erythematosus**

  Systemic lupus erythematosus (SLE) syndrome is often found associated with deficiency in C1q, C1r and C1s . SLE in humans is characterized by fever, rash, glomerulonephritis and, sometimes, hemolytic anemia.
- **3- Bacterial Infections** There are hardly any known deficiencies of Factor B and Factor D. However, properdin deficiency is known and is associated with mortality from Neisseria meningitides. Factor I deficiencies are rare and lead to recurrent bacterial infections.