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# Complement Alternative Pathway Disease Diagnosis With an Opinion

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## Introduction

Atypical hemolytic uremic syndrome, C3 glomerulonephritis, and dense-deposit disease, as well as atypical postinfectious glomerulonephritis, are all kidney illnesses caused by aberrant modulation of the complement alternative pathway. Despite their clinical differences, they are all caused by a lack of surface or fluid-phase complement control induced by acquired or hereditary abnormalities in the complement alternative route. As a result, the diagnostic approach is comparable, with a thorough biochemical, genetic, and pathologic examination of the complement pathway. Functional activity measures of the complete complement pathway, functional and quantitative analysis of specific components and regulators, and quantification of activation products are all part of the biochemical test battery. To rule out thrombotic thrombocytopenic purpura in individuals with thrombotic microangiopathy, ADAMTS-13 activity should be measured. The range of genes that are now known to be implicated in alternate route pathogenesis Disorders are quickly spreading. A pathologic examination of an Adhoc kidney biopsy specimen is complex Laser micro-dissection and immunofluorescence studies using mass spectrometry, the determination of the inherent flaw in the alternative route based on this. A thorough examination will allow treatment to be targeted to the location of dysregulation.

## Description

A variety of renal disorders are caused by uncontrolled activation of the complement alternative pathway (AP). Atypical hemolytic uremic syndrome (aHUS) is a kind of primary thrombotic microangiopathy (TMA) characterised clinically by acute kidney damage, microangiopathic hemolytic anaemia, and thrombocytopenia. C3 glomerulopathy, which includes C3 glomerulonephritis (C3GN) and dense-deposit disease (DDD), is a pathologic condition characterised by dominant C3 accumulation with minimal or no immunoglobulin deposition [1]. Atypical postinfectious glomerulonephritis is a disease course in which the diagnosis of postinfectious glomerulonephritis is followed by persistent hematuria and proteinuria, as well as the development of end-stage kidney disease. Atypical postinfectious glomerulonephritis is most likely on the spectrum of C3GN and DDD.

Despite phenotypic heterogeneity, the distinguishing aetiology of these glomerular disorders is AP dysfunction. As a result, the approach to diagnosing these illnesses should be comparable. A genetic or acquired aberration in the complement system may not be clinically apparent until a triggering situation, such as infection or pregnancy, breaks the delicate balance between complement activation and restraint. To uncover the underlying faults in the AP, doctors, biochemical and genetic laboratories, and pathologists must work together. The goal of this communication is to provide a detailed description of the AP diagnostic examination in order to assist practising nephrologists in the challenging challenge of interpreting the results while avoiding the pitfalls of these tests.

### Pathway supplement

The complement system is a critical component of innate immunity, serving as a first line of defence against invading pathogens and aberrant self-derived components. The complement system is a proteolytic cascade of about 30 proteins in which serine proteases activate each other in a specific order. The complement components can be found in soluble form, known as the fluid phase [2], or expressed on the cell membrane, known as the solid phase. The complement system has three unique activation pathways: classical, lectin, and alternative. Each of these paths leads to the key phase of the complement system, the cleavage of C3 by C3 convertases. C3a and C3b cleavage products then initiate downstream effector actions. Opsonization, anaphylatoxin-mediated inflammation, and the development of a terminal membrane attack complex are critical effector stages. To avoid self-harm, strict active control systems are essential.

### Activation of the complement pathway

The contact between C1q and immunocomplexes, comprised of a single IgM or at least two IgG1-3 subclass molecules and the antigen, initiates the cascade in the conventional pathway. C1q contains six binding sites for constant immunoglobulin (Fc) segments of IgM or IgG. By attaching to the C1q-immunoglobulin complex, the serine proteases C1r and C1s are activated. Initially, one C1r molecule attaches and autoactivates, cleaving a second C1r molecule and both C1s molecules. C4 is cleaved by activated C1s into C4a and C4b, whereas C2 is cleaved into C2a and C2b. The C4b fragment mixes with the target cell's lipid bilayer and C2a to generate the C3 convertase of the traditional pathway, C4b2a [3].

### Enhance route effector functions

The addition of another C3b to the C3 convertases initiates the terminal complement pathway, which leads in the creation of C5 convertases—either C4bC2aC3b or C3bBbC3b. C5a and C5b are formed when these compounds split undamaged C5. C5b-9, or membrane assault complex, is formed by the sequential interaction of C5b with C6, C7, C8, and finally C9. This complex breaks cell membranes and kills cells by producing lytic holes. C3 and C5 cleavage products, C3a and C5a, are potent anaphylactotoxins. Through G protein-coupled receptors, C3aR and C5aR, they mediate local inflammation, stimulate chemotaxis, and activate cells.

### Regulation of the complement pathway

Complement factor I (FI) is a serine protease that primarily functions as a downregulator of the AP C3 convertase by proteolytically inactivating C3b to iC3b (inactive C3b) and producing C3 breakdown products C3d and C3g.

These pieces are thought to be physiologically inactive. FI's proteolytic activity is dependent on various cofactors, including complement factor H (FH), membrane cofactor protein (MCP, CD46), and decay-accelerating factor (DAF, CD55). DAF and MCP are membrane-bound regulators that speed up the degradation of the C3 convertase by allowing Bb to dissociate from C3bBb [4].

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### Biochemical evaluation

Complement analysis today extends much beyond the usual determination of C3 and C4. To begin, a functional activity test of the classical and alternative routes may reveal whether or not the pathways are intact. Second, examining individual components and regulators may reveal functional or quantitative flaws in specific aspects. Third, quantification of activation products provides an estimate of the pathways' activation state and establishes whether a complement factor is lowered due to increased consumption or decreased production [5]. To exclude out thrombotic thrombocytopenic purpura in patients with TMA, ADAMTS-13 activity should be measured (TTP).

Because soluble complement component assays are prone to pre-analytical mistakes, adequate sample acquisition and handling are critical. After the sample has been acquired, precautions must be taken to avoid continuous in vitro complement consumption. This requirement necessitates immediate ice transfer from the clinic to the laboratory, fast centrifugation, and storage at -20 C or -70 C. (all typically within 30 minutes of the blood draw). Furthermore, samples should be taken prior to the start of plasma therapy. Serum is collected in plain tubes [6], plasma in ethylenediamine tetraacetic acid tubes (the ethylenediamine tetraacetic acid hinders continuous complement action), and citrated plasma in citrate-containing tubes (for ADAMTS-13 activity testing). Abnormal functional testing results that contradict the clinical history should be confirmed [7].

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C4 deficiency is not uncommon in families. The gene has two isotypes: C4A and C4B. The former forms amide connections with immunological aggregates or protein antigens more efficiently, whereas the latter generates ester bonds with carbohydrate antigens. 50% to 65% of persons have two copies of C4A and C4B, and 35% have gene deletions or duplications of C4A, C4B, or both, resulting in 1 to 8 functioning C4 genes. C4 levels are borderline in about 1% to 3% of European Americans. This genetic discovery is linked to an increased risk of systemic lupus erythematosus, scleroderma, IgA nephropathy, Henoch-Schönlein purpura, and membranous nephropathy (w10% of European American systemic lupus erythematosus patients are C4A deficient).

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## Conflict of interest

None declared.

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