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EDUCATIONAL REVIEW

C3 Glomerulopathy

Magdalena Riedl[1,2] · **Paul Thorner**[3,4] · **Christoph Licht**[1,5,6]

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Abstract Recent advances in our understanding of the disease pathology of membranoproliferative glomerulonephritis has resulted in its re-classification as complement C3 glomerulopathy (C3G) and immune complex-mediated glomerulonephritis (IC-GN). The new consensus is based on its underlying pathomechanism, with a key pathogenetic role for the complement alternative pathway (AP), rather than on histomorphological characteristics. In C3G, loss of AP regulation leads to predominant glomerular C3 deposition, which distinguishes C3G from IC-GN with predominant immunoglobulin G staining. Electron microscopy further subdivides C3G into C3 glomerulonephritis and dense deposit disease depending on the presence and distribution pattern of electron-dense deposits within the glomerular filter. Mutations or autoantibodies affecting the function of AP activators or regulators, in particular the decay of the C3 convertase (C3 nephritic factor), have been detected in up to 80 % of C3G patients. The natural outcome of C3G is heterogeneous, but 50 % of patients progress slowly and reach end-stage renal disease within 10–15 years. The new classification not only marks significant advancement in the pathogenic understanding of this rare disease, but also opens doors towards more specific treatment with the potential for improved outcomes.

Keywords C3 Glomerulopathy · Membranoproliferative glomerulonephritis · Complement · Dense deposit disease · C3 Nephritic factor · Eculizumab

Abbreviations

aHUS	Atypical haemolytic uremic syndrome
AP	Alternative pathway (of complement)
C3	Complement component 3
C3G	C3 Glomerulopathy
C3GN	C3 Glomerulonephritis
C3NeF	C3 Nephritic factor
CFH	Complement factor H
CFHR1–5	Complement factor H-related proteins 1–5
CP	Classical pathway (of complement)
DDD	Dense deposit disease
ESRD	End-stage renal disease
GN	Glomerulonephritis
IC	Immune complex
MCP	Membrane-cofactor protein/CD46
MPGN	Membranoproliferative glomerulonephritis
PIGN	Post-infectious glomerulonephritis
TMA	Thrombotic microangiopathy

Introduction

The deposition of immunoglobulins (Ig)/immune complexes (IC) and/or complement proteins in the mesangium and/or

✉ Christoph Licht
christoph.licht@sickkids.ca

[1] Cell Biology Program of the Research Institute, The Hospital for Sick Children, 555 University Avenue, Toronto, ON M5G 1X8, Canada

[2] Department of Paediatrics, Innsbruck Medical University, Innsbruck, Austria

[3] Department of Pediatric Laboratory Medicine, The Hospital for Sick Children, Toronto, ON, Canada

[4] Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada

[5] Division of Nephrology, The Hospital for Sick Children, Toronto, ON, Canada

[6] Department of Paediatrics, University of Toronto, Toronto, ON, Canada

along the capillary walls of the glomerulus results in mesangial/endocapillary proliferation and capillary-wall remodelling with the formation of double contours. Until recently, these light microscopy-based features were used as diagnostic criteria for membranoproliferative glomerulonephritis (MPGN) [1, 2]. The increasing understanding that MPGN is caused by two different mechanisms has recently resulted in a re-classification of MPGN into: (1) a complement-mediated C3 glomerulopathy (C3G) with predominant C3 deposition, and (2) an Ig/IC-mediated glomerulonephritis (IC-GN) with mainly IgG staining on immunohistochemistry [2, 3]. In the new classification, a previous diagnosis of MPGN I reflects either C3G or IgG/IC-mediated GN, depending on the C3 staining. Patients with MPGN II or dense deposit disease (DDD) are re-classified as C3G. This new approach also allows cases with C3 deposition to be classified irrespective of glomerular lesions on light microscopy [3]. Predominant C3 staining is defined as a C3 staining intensity of≥2 orders of magnitude more than any other immune reactant (e.g. IgG/IgA, C1q) using a scale ranging from 0, trace, 1+ to 3+ [3]. Ig/IC deposition in the kidney is very likely the result of an identifiable cause (secondary MPGN), such as infections, autoimmune diseases, malignancies and monoclonal gammopathy (Table 1) [4–6]. C3G is considered to be a primary complement disease, where complement deposition results from defective control of the alternative pathway (AP) of complement [7, 8]. Of note, complement activation—primarily of the classical pathway (CP)—also occurs in Ig/IC-mediated GN [9].

Proteinuria, haematuria, arterial hypertension and low C3 are possible clinical symptoms indicative of C3G; the final diagnosis, however, is solely based on kidney biopsy. Further diagnostic workup and treatment depend especially on immunohistochemistry findings in combination with light and electron microscopy findings [3]. Treatment concepts now include targeting the complement system in C3G and immunosuppressive treatment in Ig/IC-mediated GN. However, major challenges remain as clinical trials and treatment guidelines are missing. Furthermore, the clinical course of C3G is heterogeneous, and the fact that some patients may recover without treatment has to be considered. In this review we focus on C3G, but concede that available literature is mainly based on the traditional nomenclature, which we have interpreted as best as possible in light of the new consensus guidelines.

Table 1 Causes of secondary membranoproliferative glomerulonephritis

Causes of secondary membranoproliferative glomerulonephritis
Infectious diseases: bacterial/viral/protozoal
• Hepatitis B, C; Epstein–Barr virus; human immunodeficiency virus
• Endocarditis/visceral abscesses
• Infected ventriculoatrial shunts/empyema
• Malaria, schistosomiasis, mycoplasma
• Tuberculosis, leprosy
• Brucellosis
Systemic immune diseases
• Cryoglobulinaemia
• Systemic lupus erythematosus
• Sjögren's syndrome
• Rheumatoid arthritis
• Heriditary deficiencies of complement components
• X-linked agammaglobulinemia
Neoplasms/dysproteinemias
• Plasma cell dyscrasia
• Fibrillary and immunotactoid glomerulonephritis
• Light-chain deposition disease
• Heavy-chain deposition disease
• Light- and heavy-chain deposition disease
• Leukaemias and lymphomas (with cryoglobulinaemia)
• Waldenstrom macroglobulinemia
• Carcinomas, Wilms' tumor, malignant melanoma
Chronic liver disease
• Chronic active hepatitis (B, C)
• Cirrhosis
• Alpha-1-antitrypsin deficiency
Miscellaneous
• Thrombotic microangiopathy
• Sickle cell disease
• Partial lipodystrophy
• Transplant glomerulopathy
• Niemann–Pick disease (Type C)

Histopathology

C3 Glomerulopathy consists of the two entities, namely, C3 glomerulonephritis (C3GN) and DDD [3, 10]. On kidney biopsy C3GN and DDD present as a proliferative GN. The most common patterns on light microscopy comprise that of a membranoproliferative GN, a diffuse proliferative GN, mesangial proliferative GN or even a necrotizing and crescentic GN [3, 11]. Immunohistochemistry studies show predominant C3 staining in both subtypes, and therefore electron microscopy is needed to differentiate C3GN from DDD. In C3GN, discrete C3 deposits are located in the mesangium and along the capillary wall, whereas in DDD C3 deposits are more intense and located in the mesangium and within the glomerular basement membranes where they form a unique ribbon-shaped band (Fig. 1) [10].

By contrast, post-infectious GN (PIGN), a major differential diagnosis of C3G, is characterized by mesangial C3 along with intense IgG deposition and additional mesangial

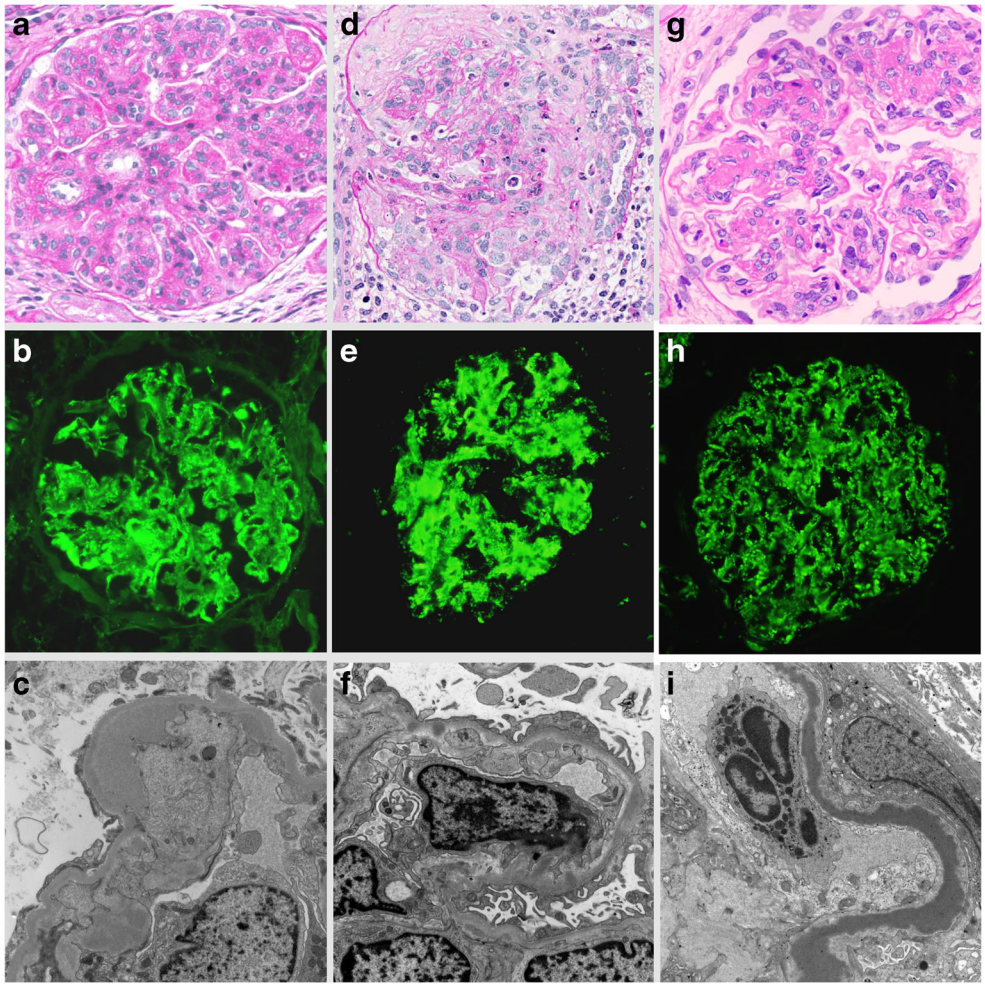

Fig. 1 Histopathological findings in complement 3 glomerulopathy (C3G). *Panels* highlight the microscopic features of membranoproliferative glomerulonephritis (GN) type I (**a**–**c**), C3 glomerulopathy (**d**–**f**), and dense deposit disease (DDD) (**g**–**i**) by light microscopy (*top row*), immunofluorescence (*middle row*) and electron microscopy (*bottom row*). **a**–**c** Typical membranoproliferative GN results in a cellular glomerulus with expanded mesangial regions resulting from increased matrix and cellularity, as well as immune complex (IC) deposition. Capillary loops are thickened with narrowed lumina from enlarged endothelial cells, mesangial interposition and IC deposition. There is strong staining for both immunoglobulin G (IgG) and C3 by immunofluorescence (only IgG is shown). By electron microscopy, capillary loops show prominent subendothelial deposits and mesangial interposition. **d**–**f** C3G can have a wide spectrum of appearances, ranging from mesangial proliferative, membranoproliferate, to a necrotizing crescentic GN (illustrated here). C3 deposition predominates by immunofluorescence. By electron microscopy, IC deposition may be scanty (as illustrated here), but can include large subepithelial and/or subendothelial deposits, with or without mesangial interposition (also seen here). **g**–**i** DDD imparts a uniform ribbon-like appearance to the glomerular basement membrane, highlighted here by Periodic acid–Schiff (PAS) staining. Mesangial regions show increased matrix and cellularity, but mesangial interposition along capillary loops is an inconsistent feature. C3 deposition can be detected by immunofluorescence, although usually the deposition is less than that seen in C3G. Electron microscopy findings are diagnostic with the presence of an intramembranous electron-dense alteration to the basement membranes along capillary loops and sometimes in mesangial regions. Early in the disease, this change involves loops only partially, but it becomes confluent as the disease progresses. **a**, **d**, **g** PAS staining, original magnification ×400; **b** IgG, original magnification ×400; **e**, **h** C3, original magnification ×400; **c**, **f**, **i** original magnification ×10000

subendothelial and subepithelial humps [3, 12–14]. While all patients in one study had normal serum C4 levels [12], C4d staining served well to differentiate patients with C3G and patients with proliferative GN including PIGN in a different study [14]. In the latter study, a subgroup of patients clinically diagnosed with PIGN showed only the combination of C3 deposition and humps. As low C3 levels, haematuria/proteinuria or impaired renal function were persistent, and defects in the AP were identified, these patients received the diagnosis of "atypical" PIGN, possibly representing patients with C3G [12]. Infections—including streptococcal infections—are a common trigger for C3G, and humps are also discovered in biopsies of patients with C3G, thus making the differential diagnosis difficult [3, 15, 16]. Close clinical monitoring is needed, and any atypical features (above) should raise the suspicion of C3G. Re-evaluation of kidney

biopsies of our own cohort of PIGN patients resulted in 25 % of patients being re-classified to C3G. Lack of recovery of clinical symptoms and persistently low C3 levels after 6 months were characteristic features of these re-classified patients [17].

Complement—activation and regulation

The complement system is an integral part of innate immunity. Its main purpose is to complement antibodies and phagocytic cells in antimicrobial and IC clearing [18]. Defective regulation or over-activation caused by mutations or autoantibodies have been linked with a variety of renal diseases, including thrombotic microangiopathy (TMA), especially atypical haemolytic uraemic syndrome (aHUS), systemic lupus erythematosus (SLE), antibody-mediated rejection, ANCA-associated vasculitis and membranous nephropathy [19, 20].

The complement system can become induced via three pathways, each inducing a proteolytic activation cascade, leading—amongst other functions—to the formation of anaphylatoxins (C3a, C5a) and the potential lytic membrane attack complex (MAC; C5b-9). The CP is activated by immunoglobulins or immune-complexes and therefore is especially involved in autoimmune diseases and the Ig/IC-mediated form of MPGN. Mannose-binding lectin and ficolins expressed on the surface of microorganisms are now recognized as being responsible for the activation of the lectin pathway [18]. By contrast, the AP is constitutively active and therefore tightly regulated so as to maintain a balance between indispensable activation and harmful over-activation. Once switched on, all pathways merge in the activation of C3 to C3b, which is quickly deposited on target surfaces (opsonization); C3b has the potential to mobilize C5b-9 formation, which is associated with cell cytotoxicity but also with the generation of a pro-inflammatory and pro-coagulation phenotype (Fig. 2a) [18].

The alternative pathway of complement

In the AP, a process called tick-over hydrolysis activates C3, which binds activated complement factor B (CFB) to form the initiation AP C3 convertase complex, C3(H_20)Bb. Activation of CFB into Bb is a result of complement factor D (CFD) cleavage. The initiation AP C3 convertase can then enhance further C3 activation (C3a, C3b) and form the amplification AP C3 convertase (C3bBb), which serves as an amplification loop for the complement system by further augmenting C3b conversion [18]. Properdin (CFP) stabilizes the AP C3 convertase. To prevent further activation steps, such as the formation of the C5 convertase and ultimately C5b-9, regulators promote either the inactivation of C3b or the decay of the AP C3 convertase (Fig. 2b) [18].

Inactivation of C3b to iC3b and further fragments, such as C3dg and C3d, is referred to as cofactor-mediated cleavage. C3b inactivation through proteolysis is achieved by the plasma serine protease complement factor I (CFI) and its cofactors, complement factor H (CFH) in fluid phase and membrane-cofactor protein (MCP) and complement receptor 1 (CR1) on cell surfaces (Fig. 2b).

Regulators with decay-accelerating activity, accomplished by accelerating the dissociation of C3b and Bb within the AP C3 convertase, are CFH in fluid phase and decay-accelerating factor (DAF) and CR1 on cell surfaces (Fig. 2b).

Complement factor H and related proteins

Complement factor H is the key regulator of the AP. In addition to its regulatory role in fluid phase (i.e. cofactor for C3b inactivation and C3 convertase decay), CFH is the main factor preventing complement activation on cell surfaces. The C-terminal region of CFH is responsible for surface recognition, whereas the N-terminal region promotes co-factor and decay-accelerating activity [18]. It is not surprising that aHUS—a disease with uncontrolled complement activation on endothelial cells—is associated with mutations in the C-terminal region of CFH, whereas in C3G, a disease associated with defective fluid phase C3 control, mutations are detected in the N-terminal region of CFH (Fig. 2c, d) [21].

There are five proteins that show sequence and structural homology to CFH; these are therefore termed complement factor H-related proteins (CFHR) 1–5. The function of these proteins is not yet fully understood. However, CFHR1 has been recently identified as participating in controlling C5 activation [22], and CFHR1, CFHR2 and CFHR5 have been discovered to act as CFH antagonists. These proteins share a dimerization motif which allows them to form dimers and thereby compete with CFH binding and CFH-mediated regulation at physiological concentrations [23, 24].

Lessons learned from animal models

Animal models have been very helpful in facilitating a better understanding of the role of complement in C3G. The detection that Norwegian pigs with a renal disease similar to DDD carry a homozygous *CFH* mutation introduced the concept of uncontrolled complement activation in C3G and was the first, naturally occurring, animal model for DDD [25]. A similar phenotype was accomplished in mice genetically engineered for CFH deficiency ($cfh^{-/-}$). Biopsies revealed deposits within the glomerular basement membrane accompanied by C3 and C9 deposits, systemic hypocomplementemia and a high mortality rate [26]. A key role of the AP was identified when mice genetically deficient in CFB were rescued from the DDD phenotype [26]. The development of C3 deposits in a $cfh^{-/-}$ mouse

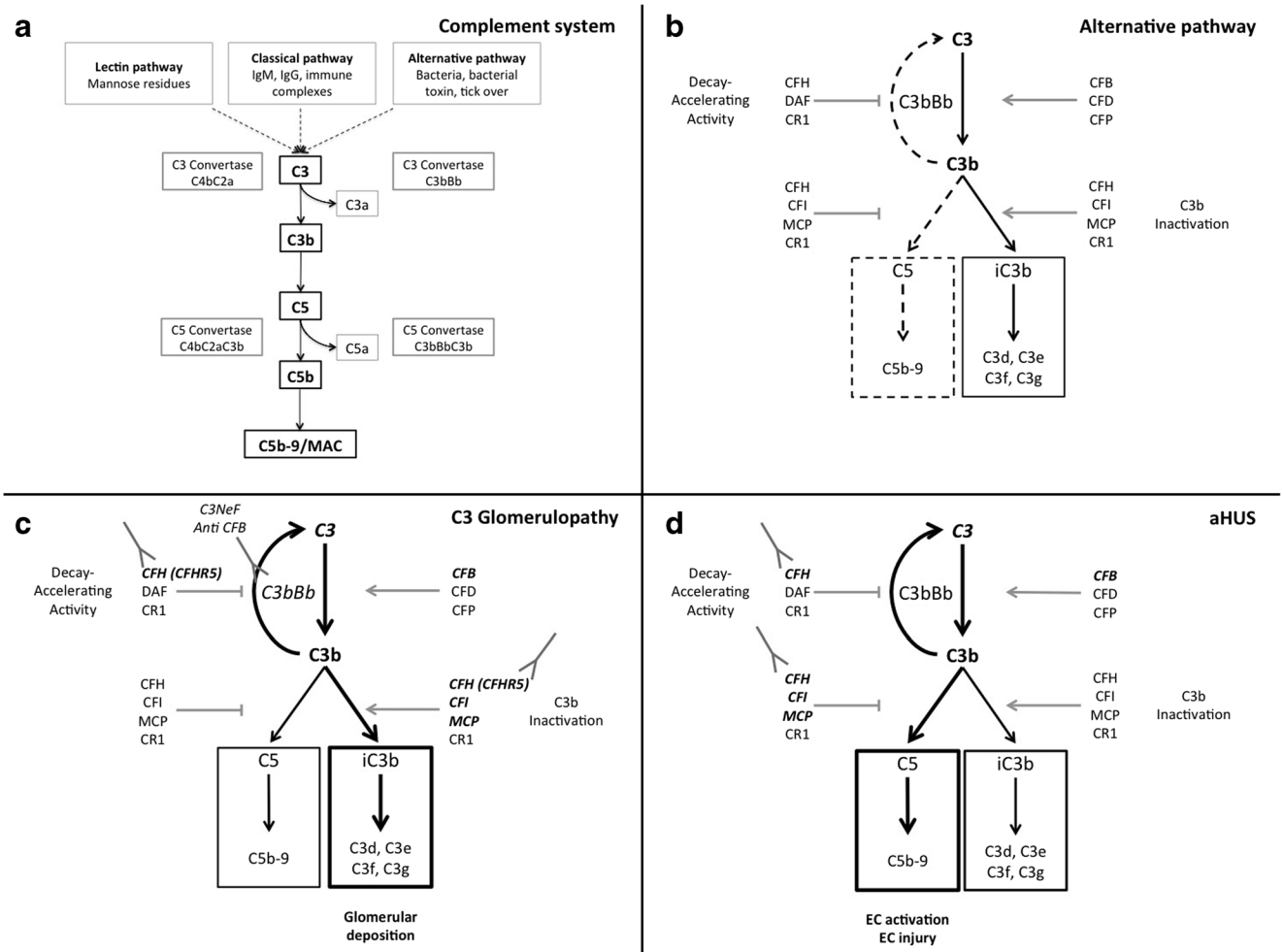

Fig. 2 Complement activation, regulation and disease specific dysfunction. **a** The three activation pathways of complement, namely, the classical (CP), the mannose binding lectin and the alternative (AP) pathway, merge in the activation of C3 to C3b via (CP and/or AP) C3 convertase. C3b promotes the formation of a C5 convertase to activate C5 to form the anaphylatoxins C5a and C5b, which initiate the terminal pathway, resulting in the assembly of the C5b-9 or membrane attack complex (*MAC*) on cells and in turn resulting in cell injury, inflammation and thrombosis. **b** The AP is tightly regulated. Complement factors B and D (*CFB*, *CFD*) and CFP (properdin) participate in the formation of the alternative C3 convertase, generating C3b. C3b can engage into an amplification loop of C3 activation. This step is regulated in fluid phase by CFH and on cell surfaces by CD35/CR1 and decay accelerating factor (*DAF*/*CD55*). The fate of C3b on cell surfaces is determined by fluid phase and surface-bound regulators. Fluid phase (*CFH*, *CFI*) and membrane-anchored cofactor protein (*MCP*/*CD46*, *CR1*) regulators generate the inactive iC3b and further C3b split products (*C3d*, *C3e*, *C3f*, *C3g*), thereby preventing terminal complement activation (*C5*, *C5b-9*). *Solid lines* physiological pathways, *dotted lines* pathways suppressed by regulators. **c**. In C3G mutations and autoantibodies (*italics* and *bold font*) predominantly affect fluid phase regulators, resulting in excess formation of activated C3 (*C3b*) and its split products, which can be deposited in the glomerulus. Activation of the terminal pathway was detected in a subgroup of patients with C3G. *Bold and thick lines* Pathological complement activation in C3G. **d**. In atypical haemolytic uraemic syndrome (*aHUS*) mutations and antibodies (*italics and bold font*) impair complement control on the endothelial surface, resulting in terminal pathway activation, endothelial cell injury and thrombus formation

is dependent on the CFI-mediated generation of C3b inactivation products, as evidenced by *cfh*$^{-/-}$ mice which also lack CFI (*cfh*$^{-/-}$, *cfi*$^{-/-}$) developing mild mesangial C3 deposits only, but precipitating the full C3G phenotype when serum was infused to restore the CFI pool [26, 27]. The role of the terminal complement pathway was studied by using *cfh*$^{-/-}$;*C5*$^{-/-}$ mice: after 12 months these mice showed decreased mortality, less inflammation and better renal function than *cfh*$^{-/-}$ mice, indicating that there is a contribution of the terminal pathway in C3G [28]. Of note, a TMA phenotype was achieved in this model only if solely the surface recognition part of CFH [short consensus repeat (SCR)16-20] was lacking. The TMA phenotype was completely rescued by inhibiting the terminal complement pathway when C5 was abolished [29, 30].

Lessons learned from patients

Complement component 3 deposition in the kidney and systemic C3 consumption are hallmark features of C3G. Results from detailed genetic and autoimmune workups haves strengthened the notion that the complement AP plays a major role in C3G, where mutations or circulating autoantibodies result in the loss of control of the complement AP C3 convertase (Fig. 2b, c). The mechanisms involved include (Fig. 2c):

- Autoantibodies stabilizing the decay of the AP C3 convertase [C3 nephritic factor (C3NeF)] [31]
- *CFH* mutations or CFH autoantibodies resulting in loss of function and therefore impaired regulation of the decay of the complement AP C3 convertase [32]
- *C3* and *CFB* mutations resulting in an extremely stable complement AP C3 convertase resistant to its decay [33].

The consequence of all of these mechanisms is an enhanced activation rate of C3, although an increased formation of the terminal pathway of complement was also detected in patients with C3G [34]. This increased C3 turnover results in C3 consumption and systemic hypocomplementemia as well as the generation of C3b inactivation products, deposited within the kidneys (Fig. 2c). Although the same proteins are affected in aHUS, their functional consequences can vary. In aHUS, mutations result predominantly in terminal pathway activation, with the formation of the C5b-9/MAC complex causing endothelial cell injury (Fig. 2d).

The role of complement was further supported by recent work by Sethi *et al*., who were able to confirm the occurrence of proteins of the alternative and terminal pathway of complement in the glomerulus of C3G patients using mass spectrometry [7, 8]. CFB was not detected, and the authors therefore concluded that the complement AP activation occurred systemically (in fluid phase) but not locally (on surfaces).

Autoimmune forms

In 1965 Spitzer et al. described a substance in the serum of patients with GN that cleaved C3 [35]. This antibody was subsequently named C3 Nephritic factor (C3NeF) and characterized as binding and stabilizing the AP C3 convertase, therefore enhancing C3b production via the amplification loop (Fig. 2c); in two separate studies, C3NeF was detected in 86 % of DDD and 46 % of C3GN patients and associated with lower C3 levels [21, 36]. C3NeF can fluctuate during the clinical course without any correspondence to disease activity and treatment [36, 37]. In one case, C3NeF was reported to disappear after renal transplantation [38]. As C3NeF is heterogeneous, a reliable detection is challenging, and efforts aiming at establishing a consensus for the detection of C3NeF are currently underway (V. Fremeaux-Bacchi and M. Kirschfink, personal communication).

C3NeF has also been discovered in other renal diseases, such as SLE [39, 40], PIGN [12], meningococcal meningitis [41] and also in healthy individuals [31]. The finding of C3NeF does not exclude the co-existence of complement mutations, and despite C3NeF positivity a full C3G investigation (Table 2) should be performed [42].

Other auto-antibodies resulting in the loss of complement AP C3 convertase control, such as anti-CFB and anti-C3b antibodies, have been reported (Fig. 2c) [43]. Strobel et al. reported an antibody binding to CFB and Bb in a patient with DDD, who additionally had decreased terminal pathway activation by inhibiting the C5 convertase [44]. Factor H antibodies are frequently (up to 25 %) associated with aHUS where they act by blocking C3b binding of CFH [45], and in rare cases they are associated with MPGN where they act by inhibiting CFH function [46].

One report by Sethi et al. describes a girl with proliferative GN and dense deposits without C3 staining but intense C4d staining. The authors confirmed that the deposits were positive for C4 [47]. A C4 nephritic factor (C4NeF) has already been described earlier in patients with MPGN, also in combination with a C3NeF [48]; patients with both auto-antibodies had the worst clinical outcome [48]. However, recent cohorts have not been screened for C4NeF, and its role and functional implications are still unclear.

Genetic forms

In one study, complement mutations and rare variants were detected in patients with MPGN I (17 %), C3G (17 %) and DDD (20 %), respectively [21]. Several studies have reported complement mutations in the following complement genes: *CFH*, *CFI*, *MCP*, *CFB* and *C3* [21, 32, 33, 49–54].

Table 2 Diagnostic workup in patients with complement component 3 glomerulopathy

Global complement function	CH50, APH50
Complement activation	C3, C4, C3d
Terminal pathway activation	SC5b-9
Complement protein levels	CFH, CFI, CFB
Autoimmune forms	C3 Nephritic factor (C3NeF) CFH/CFB/C3b autoantibodies
Genetic forms	Mutations/CNVs in CFH, CFI, CFB, MCP/CD46, C3 CFHR–5 (MLPA)

CH50, Total haemolytic complement assay; APH50, alternate pathway activity of complement assay; C3, complement component 3; CF, complement component factor; CNV, Copy number variation; CFHR, complement factor H related-protein; MLPA, multiplex ligation-dependent probe amplification

Additional mutations or internal duplications in CFHRs or the formation of hybrid genes have also been associated with MPGN (Table 3; Fig. 2c) [23, 55–58], and risk haplotypes have been identified in *CFH*, *C3* and *MCP* [21, 24, 59–62]. In two studies, the presence of two or more complement haplotypes increased the odds of developing the disease [21, 61]. Table 3 gives an overview of mutations, rare variants and polymorphisms associated with C3G. Interestingly, several mutations had been previously described in patients with aHUS [21]. Compared to aHUS, mutations in CFH associated with C3G are rather located in the N-terminal region of CFH and represent a quantitative deficiency up to CFH null phenotype [21, 32, 63].

Deletions of *CFHR3/CFHR1* were discovered, but are - unlike in aHUS - not associated with CFH antibodies [43]. Most *CFI* mutations associated with MPGN had already been reported in patients with aHUS, with the functional consequences in fluid phase remaining unclear [21].

In 2009 Gale *et al*. described a mutation in CFHR5 in patients of Cypriotic origin with unexplained renal disease [55]. However, the role of CFHRs in C3G remained unclear until Goicoechea de Jorge *et al*. reported that in dimer form CFHR1, CFHR2 and CFHR5 compete with CFH for C3b binding, thus protecting C3b from inactivation and the complement AP C3 convertase from decay. This process, termed *deregulation*, was reported to be increased in patients with a *CFHR1-3* hybrid gene and a CFHR5 mutation comprised of a duplication in the dimerization domain [23, 55, 57].

Epidemiology and clinical presentation

Membranoproliferative glomerulonephritis or C3G are rare diseases with an estimated incidence of 1–2 per million per total population [64, 65]. Patients with C3G present with a variety of symptoms, ranging from a mild disease with asymptomatic microhaematuria and/or proteinuria to a severe disease with nephritic or nephrotic syndrome and renal impairment. The kidney is the major target, possibly due to the morphological specificities of the glomerular capillaries, in

Table 3 Mutations associated with C3 glomerulopathy

Gene/protein	Mutation/variant	Function	Phenotype	Reference
CFH	Mutations • Homo-/compound heterozygous • SCRs 1-4 (regulatory domain) • Cys residues (tertiary structure)	• Intact surface binding • Reduced C3b binding • Loss of CFH cofactor and decay accelerating activity	DDD/C3G	Levy et al. [50] Vogt et al. [53] Ault et al. [51] Dragon-Durey et al. [52] Licht et al. [32] Habbig et al. [49]
CFH	Polymorphisms • Y402H (SCR 7)	• Impaired C3b/heparin binding • Impaired CFH cofactor activity	DDD	Hageman et al. [60] Abrera-Abeleda et al. [59] Abrera-Abeleda et al. [61]
CFI	Type I and II	• Decreased activity on cell surface	DDD/C3GN	Servais et al. [21]
MCP/CD46	Rare SNP	• Defective control on cell surface	C3GN	Servais et al. [21]
CFHR1	Internal duplication	• Alters FHR oligomerization • Greater degree of CFHR-mediated deregulation	DDD	Tortajada et al. [58]
CFHR3-1	CNV • CFHR3-1 hybrid gene	• Greater degree of CFHR-mediated deregulation	C3G	Malik et al. [57] Goicoechea de Jorge et al. [23]
CFHR5	CNV • Duplication in CFHR5 exons 2/3	• Greater degree of CFHR-mediated deregulation	C3G	Gale et al. [55] Goicoechea de Jorge et al. [23]
CFHR5	Polymorphisms	• Not tested	DDD	Abrera-Abeleda et al. [59] Abrera-Abeleda et al. [61]
CFHR2–5	CFHR2–CFHR5 hybrid gene	• Stabilizes C3 convertase, reduced CFH mediated decay	DDD	Chen et al. [56]
C3	Mutations: • Heterozygous deletion	• $C3_{mut}$ - resistant to cleavage by C3bBb • $C3_{mut}$ convertase - resistant to CFH inactivation, normal MCP/CD46 regulation	DDD	Martinez-Barricarte et al. [33]
C3	Polymorphisms	• Not tested	DDD	Smith et al. [62] Abrera-Abeleda et al. [61]
CFB	Mutations: • Heterozygous	• Not tested	C3GN	Imamura et al. [54]

DDD, Dense deposit disease; MCP, membrane-cofactor protein; SCR, short consensus repeat; SNP, single nucleotide polymorphism

particular the fenestrated endothelium, with exposure of the glomerular basement membrane to serum (complement). Although low levels of C3 are considered a hallmark feature of C3G, in one study low C3 levels were only detected in about 50 % of the patients [21]. Therfore, a normal C3 level does not rule out C3G [21].

The clinical presentation does not allow a differentiation between C3GN and DDD, although some differences have been reported. For example, patients with DDD show an earlier presentation (59 % <16 years of age at diagnosis) compared to patients with C3GN where only 25 % present in childhood and adolescence. Several studies have reported a slight predominance of male patients for both DDD and C3G (59 vs. 41 %) (Table 4) [21, 65, 66].

In one study, low levels of C3 were detected in 59 % of patients with DDD but only in 40 % of patients with C3GN. The lowest C3 levels were associated with the finding of a C3NeF. In the same study, low C4 levels, commonly seen in patients with SLE, were reported in 4.5 % of DDD patients [21].

Extrarenal manifestations and complications

Extrarenal manifestations, such as acquired partial lipodystrophy (aPL) and ocular C3 deposits are uncommon in C3G. Ocular deposits are similar to the soft drusen seen in age-related macular degeneration (AMD) [60]. Interestingly, polymorphisms in complement genes are also associated with the risk of developing AMD [67]. These drusen consist of C3 split products and CFH [68, 69]. aPL usually precedes the diagnosis of MPGN and may present with low C3 levels and C3NeF. It is presumably caused by complement dysregulation on adipocytes [70, 71].

Table 4 Clinical presentation and outcome of patients with dense deposit disease and C3 glomerulopathy[a]

Clinical presentation/clinical outcome	Dense deposit disease	C3 glomerulopathy
Paediatric onset (<16 years)	43–70 %	25–54 %
Mean age at onset (years)	19 ± 18	30 ± 19
Clinical presentation		
Nephrotic syndrome	38–43 %	27–44 %
Microhaematuria	76–84 %	65 %
Arterial hypertension	21–60 %	40 %
Impaired renal function (>1.5 mg/dL creatinine)	29 %	50 %
Low C3 (<75 mg/dL)	59–79 %	40–48 %
Long-term outcome		
Duration to end-stage renal disease (years)	10 ± 11	11 ± 10

[a] Adapted from Servais [20], Lu [63] and Medjeral-Thomas [62]

TMA has been reported in patients with MPGN and can occur before and after MPGN diagnosis, prior to and after transplantation due to MPGN and also within a pedigree of members affected with aHUS [21, 72–75]. In a French cohort, TMA was observed in 17 % of patients with MPGN I after transplantation [21]. This overlap resulted in the creation of the term of a spectrum of complement-mediated renal diseases, recently discussed elsewhere [19]. Surprisingly, this spectrum was only associated in one out of six patients with a complement mutation [21].

Diagnosis

The diagnosis C3G should be considered in patients with: (1) nephritic syndrome, (2) nephrotic syndrome and (3) proteinuria and/or haematuria or (4) unclear deterioration of renal function. Low C3 level is very indicative of C3G, especially if evidence for PIGN is lacking. The definitive diagnosis is made by light and electron microscopic evaluation of a kidney biopsy. Diagnostic workup consists of a step-wise approach aimed at: (1) excluding differential diagnoses, (2) excluding secondary MPGN and (3) detecting causes of complement activation (Table 2). A detailed history should include a possible familial history of C3G and Ig/IC-mediated glomerulonephritis, aHUS or unclear renal insufficiency, prior episodes of unclear haematuria and or proteinuria and secondary causes, such as infections, autoimmune diseases and paraproteinemia.

Differential diagnosis

Proteinuria/haematuria or nephrotic and nephritic syndrome are associated with a variety of other kidney diseases, such as PIGN, IgA neuropathy (IgAN) and lupus nephritis. The latter preferentially occurs in adolescent females with the concomitant finding of low C4. The occurrence of preceding infections and low C3 levels in both C3G and PIGN makes the differential diagnosis difficult, and even a kidney biopsy might not suffice to distinguish these entities, as humps also occur in C3G [12]. However, patients with C3G are reported to have lower C3 levels than patients with lupus nephritis, and in PIGN the C3 levels are expected to normalize within 8–12 weeks [76]. A positive familial history and lack of normalization of C3 within 12 weeks favours the diagnosis of C3G. For every atypical PIGN patient, long-term follow-up with urine screening for proteinuria and haematuria is advised to identify disease progression and/or recurrence. Recurrent macroscopic haematuria occurs during banal intercurrent infections and may be related to IgAN, which can be differentiated on biopsy [77].

Treatment and outcome

Treatment standards for patients with MPGN or C3G are lacking, and commonly used treatment algorithms are based on single-centre studies and expert opinions. Current treatment recommendations consist of immunosuppressive and anti-complement therapy as well as anti-proteinuric and reno-protective therapy.

Supportive therapy

Angiotensin-converting-enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) are used in many patients with proteinuric kidney diseases due to their anti-proteinuric and anti-hypertensive effect. The authors of one study reported that better renal survival was associated with the use of ACEI or ARBs in patients with MPGN [21]. Otherwise, routine clinical care should follow current best practice guidelines for the management of arterial hypertension and end-stage renal disease (ESRD).

Immunosuppressive treatment

Several studies report the use of prednisone in MPGN in children [78–80]. In one study, long-term low dose prednisone was associated with a beneficial effect on proteinuria and long-term renal function [80]. However, only a subgroup of MPGN I patients—now classified as C3GN and Ig/IC-mediated GN—will respond, and this response might only be partial [80]. Therefore, prednisone is considered a first line agent only for patients with Ig/IC-mediated GN who present with nephrotic-range proteinuria with or without renal failure. No beneficial effect has been detected in patients with DDD.

Mycophenolat mofetil (MMF) was administered alone or in combination with steroids in idiopathic MPGN and generated encouraging results in a small case series where the addition of MMF to the therapeutic regimen of 13 patients with steroid-resistant primary MPGN resulted in sustained improvement of proteinuria and renal function within 1 year [81]. In another study involving 51 patients with primary glomerulonephritis, including 15 patients with MPGN, a partial or complete remission was reported in 70 % of patients after 1 year [82]. In another study, treatment with MMF and prednisone for a mean time of 40 months resulted in complete or partial response in five of nine children with MPGN I. However, all patients with low C3 levels did not improve in terms of clinical symptoms [83]. No specific reports on the benefit of MMF in patients with DDD are available.

Calcineurin inhibitors (CNIs), such as cyclosporine and tacrolimus, are especially used in prednisone-resistant MPGN patients. In a small trial of 18 patients with refractory MPGN, cyclosporine in combination with low-dose prednisone induced long-term (2 years) reduction of proteinuria and stable renal function in 94 % of the patients, with a recurrence reported in one patient after treatment discontinuation [84]. In a study of 11 adult patients with steroid resistance, of whom five were also non-responsive to cyclophosphamide, tacrolimus (initial target trough level of 5–10 ng/ml) alone or in combination with prednisone in six patients resulted in partial/complete remission in nine patients [85, 86]. In two children with MPGN and suboptimal response to long-term prednisone, a rapid and complete remission was achieved with tacrolimus [87]. In contrast, CNIs have been reported not to be beneficial in DDD [88].

The detection of C3NeF has prompted the use of a B-cell-depleting agent, such as rituximab, a chimeric monoclonal CD20 antibody. Case reports in patients with MPGN type I and an immune complex-mediated disease indicate partial or complete remission after administration of rituximab (in 50 % of cases in combination with steroids) in 11 of 13 patients [89–93]. Two patients with DDD did not show any change in proteinuria or renal function, despite a decrease in C3NeF level [94, 95]. Of note, both of these patients were rescued by eculizumab therapy.

Most studies conducted to date have not differentiated between C3G and Ig/IC-mediated MPGN. However, in these studies, DDD patients did not respond to immunosuppressive treatment.

Complement-targeted therapy

With the emerging role of complement in C3G, complement-targeted treatment has been administered to patients with C3G. Several case reports have been published on the use of plasma exchange (PE) in patients with MPGN I and DDD for disease manifestation and recurrence in native and kidney grafts. A partial or complete remission was achieved in 17 of 21 patients (81 %) reported in the literature [91, 96–107]. One case report also shows the successful treatment of MPGN recurrence with PE during pregnancy, with successful delivery of a healthy child [108].

In one patient with Ig/IC-mediated GN (MPGN I), PE initially caused a transient improvement of renal function and proteinuria but the patient's clinical condition later worsened to include seizures, respiratory distress and sustained anuria. Due to a *CFHR1* deletion (without CFH antibodies), low C3 and elevated SC5b-9 levels, indicating alternative and terminal complement pathway activation, the patient was switched from PE to eculizumab, which resulted in a dramatic improvement of her clinical condition, proteinuria and renal function [98].

Three case reports, including two siblings with DDD on the background of a *CFH* mutation in SCR4 and one patient with MPGN I and a *MCP/CD46* mutation were treated for >3 years with chronic infusion of fresh frozen plasma (FFP). FFP as maintenance therapy, individualized according to the patient

needs (e.g. more frequent while suffering from intercurrent infection), was able to prevent disease progression and preserve stable kidney function [32, 49, 98]. However, plasma infusion might not be sufficient as induction therapy [109].

Several reports of the successful use of eculizumab in patients with MPGN were published in 2012 [98, 110–112]. Eculizumab is a monoclonal antibody that binds C5 and therefore prevents MAC (C5b-9) assembly [113]. Although its precise role in the pathogenesis of C3G is not known, elevated SC5b-9 levels (soluble form of C5b-9) were detected in patients with C3G [34].

The reports of 13 patients with different forms of C3G treated with eculizumab have been published. Most of these were reported as single case reports but six were part of a small clinical trial [94, 98, 110–112, 114–116]. Vivarelli *et al.* reviewed these case reports and found that an improvement had been reported in ten patients, a partial response in one patient and no response in two patients [34]. These latter two case reports involved patients with C3G and DDD, respectively, in a native and transplanted kidney, and both cases had C3NeF and mutations. Although the numbers are small, a better response seems to be associated with elevated SC5b-9 levels and shorter disease duration [34]. Of note, treatment with eculizumab is not always successful (authors' personal observation).

Practical treatment recommendation

The following treatment recommendations are solely based on expert opinion. In a patient with biopsy-proven C3G (and no underlying disease) with normal renal function and no nephrotic syndrome, treatment initiation can be deferred and spontaneous recovery awaited. However, nephrotic syndrome and/or decreased renal function should prompt treatment. In C3G patients, treatment should initially aim to re-establish complement control using PE/PI or eculizumab [49, 98, 112, 117]. In particular in patients carrying a C3NeF antibody, (maintenance) therapy with MMF or Rituximab can be considered [117].

While data on treatment duration in C3G are not available, it might be prudent to continue with a new treatment for a minimum of 6 months. If partial or complete response can be achieved, treatment should not be tapered before 12 months. Reports indicate that PE/PI can be tapered (interval and/or dosage) to a maintenance level [49, 117]. Eculizumab treatment was stopped in one patient with DDD, which resulted in worsening of proteinuria and re-initiation of eculizumab [112].

Renal transplantation

Patients with MPGN I or DDD have been reported to constitute only 0.5 % of renal transplant recipients in the USA [118]. In the same cohort of almost 200,000 kidney transplants, the 10-year death-censored graft survival rate was 56.2 and 57.5 % for patients with MPGN I and DDD, respectively, which is significantly worse than that in patients with other GN diagnoses [118]. Registries have reported a recurrence rate of 55 and 50 % for DDD patients and 60, 43 and 67 % for patients with C3GN [21, 65, 119]. Disease recurrence, as cause of graft loss, was stated in 14.5 % and 29.5 % of MPGN I and DDD patients, respectively. Graft failure occurred in 50 % of patients with disease recurrence, with haematuria and proteinuria and low C3 level in 50 % of patients being the main clinical findings [119]. A recent report from the ESPN/ERA-EDTA registry indicates that there was a significantly increased risk of allograft loss for paediatric patients with DDD, namely, 67.5 %, at 5 years post-transplant [120]. In most patients treatment for recurrence did not exceed standard immunosuppressive therapy [119].

Renal transplantation in an individual with C3G should be carefully planned and only performed after detailed complement workup. In patients with an underlying complement dysfunction (i.e. mutation or antibodies) and recurrence, post-transplant complement-targeted therapy (i.e. PE; eculizumab) should be considered.

Outcome

The outcome of patients with C3G is considered to be heterogeneous, with one-half of the patients progressing slowly to ESRD and 50 % experience a recurrence after renal transplantation [21, 65, 66, 119]. No difference in the outcome in native or transplanted kidneys has been observed between patients diagnosed with C3G or DDD, and ESRD occurs in 40–50 % after 10 years in both patient groups [21, 66]. In one study, young age and female sex were associated with the highest risk for ESRD; however, in CFHR5 nephropathy, ESRD was by far more often reported in male adults [55, 66]. Although only assessed in small case series, the best predictors of outcome remain kidney function, degree of proteinuria and arterial hypertension at initial manifestation [88]. Biopsy findings associated with worse renal survival are DDD and crescentic GN [65].

Conclusion

In order to establish a diagnosis of C3G, a physician must maintain a high index of suspicion, as there is a significant overlap in clinical presentation with other renal diseases. Diagnosis is based on kidney biopsy findings, with predominant C3 staining indicating the main role of the AP in disease

pathogenesis. Complement dysfunction on the level of C3 is mainly caused by C3NeF and mutations stabilizing the complement AP C3 convertase. Despite our increasing understanding of the underlying pathomechanism in C3G, treatment recommendations are still missing. Case reports have indicated that complement-targeted therapy might be beneficial and ameliorate long-term outcome in native and transplanted kidneys.

Key summary points

- C3 glomerulopathy (C3G) is characterized by predominant C3 staining in kidney biopsy
- C3G is a primary complement disorder, caused by mutations or autoantibodies, both affecting the regulation of the alternative pathway (AP) of complement
- The clinical presentation of C3G is heterogeneous, therefore a high level of suspicion for C3G is required
- Treatment for C3G is mainly complement-targeted

Questions (answers are provided following the reference list)

1. The final diagnosis of C3G is established based on:
   a) Clinical symptoms alone
   b) Light microscopy alone
   c) Immunohistochemistry and electron microscopy
   d) Combination of clinical symptoms and light microscopy
   e) Low C3 levels alone

2. Common clinical and laboratory features of C3G do not include:
   a) Proteinuria
   b) Nephrotic syndrome
   c) Nephritic syndrome
   d) Low C3 levels
   e) Low C4 levels

3. Complement mutations and autoantibodies found in C3G patients affect mainly:
   a) C5b-9 formation
   b) Decay of C3 convertase
   c) C3a formation
   d) C1q inhibition
   e) Endothelial surface regulation

4. Treatment options commonly NOT used in C3G include:
   a) ACE inhibitors
   b) MMF
   c) Eculizumab
   d) AT2 antagonists
   e) Steroids

5. PIGN patients which might represent C3G patients show:
   a) Humps in kidney biopsy
   b) Persistently low C3 levels and continuous proteinuria and/or hematuria
   c) Streptococcal infections
   d) Predominant IgG staining in kidney biopsy
   e) Hematuria

Compliance with ethical standards

Conflicts of interest C. Licht and M. Riedl have served on Advisory Boards and/or teaching courses for Alexion Pharmaceuticals, Inc. C. Licht and M. Riedl have received travel stipends. C. Licht has received research grants from Alexion Pharmaceuticals, Inc. and is member of the Scientific Advisory Board of the Alexion sponsored International aHUS Registry.

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Answers to questions:

1: c
2: e
3: b
4: c
5: b