"Answering Letter"

No	Author (**04383208**)	Response
	Great article, well written with lots of illustrations.	Thank you sir, we appreciate your words. Thanks again.

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No.	Reviewer (**02726701**)	Response
1)	1] The manuscript is *very interesting*. Its title emphasizes Therapeutic options, but it alludes as *diagnostic issues* as well as it intents clarify the similarities & differences between C3 ass GN & Complement associated (aHUS). For this reason, I suggest to modify accordingly the *title*. At the same time, the title focuses in KTx, but, the manuscript body considers nephrological and transplant pathologies with similar emphasis.	- "Title": Complement-mediated Renal Diseases after Kidney Transplantation, Current Diagnostic and therapeutic Options in De novo and Recurrent Diseases. - Not all entities, e.g. tissue diagnosis of TMA, necessarily changed post transplantation as compared to native disease before kidney transplantation.
2)	4] Introduction: First sentence: "The complement components can be seen in biopsies of almost all types of glomerulonephritis which can be broadly divided into two main groups: (a) "complement over-activation" include IgA and immune complex MPGN". Comment: Even complement is found in the majority of IgA glomerular disease kidney biopsies, its presence is not necessary for diagnosis; in this case, it's dubious that the example of "complement over-activation" is really present in Berger ś disease.	**Introduction:** (the disease, IgA nephropathy (IgAN), not the IgA deposits). The complement components can be seen in biopsies of almost all types of glomerulonephritis which can be broadly divided into two main groups: (a) "complement over-activation" includes IgAN and immune complex MPGN
3)	5] Eighth line: Is "class is modifiable by immunosuppression in post tx period" or it is "class is *potentially modifiable* by immunosuppression in post tx period?"	- Done & highlighted.
4)	6] *Several abbreviations* not defined in the manuscript: HB, WBC, RAS, MMF	- Done & highlighted.
5)	7] Paragraph: "Extrarenal manif: of aHUS & C3G". Its redaction is confusing. It began with Drusen, a retinal finding not expected to appear in the text by most readers and that it's properly explained at the end of the paragraph. It merits to *write the paragraph again*.	*Extrarenal manifestations of aHUS and C3G: 20% of aHUS patients express extrarenal manifestations. Their relation to complement activation and TMA evolution is unclear. Drusen is rarely seen in TMA [17]. Drusen formation, that represents an accumulation of lipids and complement-rich proteins between Bruch's membrane and retinal pigmentary epithelium, is commonly reported in age-related macular degeneration but present in a much earlier age with C3G [18]. In C3G retinal drusen and acquired partial lipodystrophy have been commonly reported. The latter is most commonly encountered with C3 nephritic factors. Factor D, an essential agent for C3 convertase formation, is highly concentrated in adipocytes that undergo C3 nephritic factor-induced complement-dependent lysis [19] (please see table 3).*

6)	8] Risk of DDD recurrence: There're a lot of redaction problems in this and following subsections. Please, correct them all. E.g, in 3rd line it is "75 child" and not "75 children".	- Done & highlighted.
	9] Risk of C3GN recurrence: First sentence does not have a *verb*.	- Added & highlighted.
7)	10] The subsection "3) Hybrid CFHR3 1 gene-related C3GN. Wong et al, (2016) have recently reported a high rate of C3G recurrence in five cases [51]" is *not clear*, because it describes just the *five* recurrent cases, without even mentioning how many cases *did not recur*?	- **Five** patients received a total of **eight** kidney transplants. **Four** renal allografts had *disease recurrence* (50%), of which *three* had biopsy-proven recurrence, with time to recurrence ranging from as early as 2 weeks following living related donor transplantation to 93 and 101 months for the two remaining allografts, respectively.
8)	11] Therapy of C dysregulation-related dis: "3] EZ was firstly rep by Bomback (2012) et al, in treating 6 patients with C3G (3 with DDD and 3 with C3GN) in an *open labelled non-blind*". What does "open labelled non-blind" mean? This paragraph contains too many "improved", please, *replace some* of these words.	Eculizumab (EZ) was firstly reported by Bomback (2012) et al, in treating 6 patients with C3G (3 with DDD and 3 with C3GN) in an open labelled trial. Dose of EZ is guided by previous experience in aHUS and used for one year. Improved kidney function was observed in two patients, one patient showed partially improved proteinuria, another patient showed better histological and laboratory findings [62].
9)	12] Treatment of post-transplant TMA: "2] PE & IVIG": Which *reposition fluid* would be more appropriate? *Stored* or *fresh plasma*, *albumin*? Another one?	- Fresh frozen plasma (FFP) is advised as reposition fluid, it must be type specific and needs to be ordered in advance and thawed before use, despite higher risk of reactions; however, it replaces *all plasma constituents* and is appropriate for patients with pre-existing coagulopathy like TMA.
10)	13] "3] Belatacept, a co-stimulatory blocking agent against CD80 & CD86 surface ligands and CD28 on T cells" All of these *three* CD molecules?	3] Belatacept, a fusion protein composed of the Fc fragment of human IgG1 linked to the extracellular domain of cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), selectively inhibits T-cell activation through co-stimulation blockade [95].
11)	14] "4] EZ, an anti-C5 agent that blocks lytic C5b-9 membrane attack complex". Please, cite the *clinical trials* that supported EZ FDA approval in aHUS.	*102. Loirat C, Babu S, Furman R, Sheerin N, Cohen D, Gaber O, et al. Eculizumab Efficacy and Safety in Patients With Atypical Hemolytic Uremic Syndrome (aHUS) Resistant to Plasma Exchange/Infusion [poster]. Presented at the 16th Congress of European Hematology Association (EHA), 2011. London, UK.* *103. Loirat C, Muus P, Legendre C, Douglas K, Hourmant M, Delmas Y, et al. A Phase II Study of Eculizumab in Patients With Atypical Hemolytic Uremic Syndrome Receiving Chronic Plasma Exchange/Infusion [poster].. Presented at the 16th Congress of European Hematology Association (EHA), 2011. London, UK.*
12)	15] "Ttt of recurrent TMA:" Sent: 3 ("3] Cases with isolated "*membrane cofactor protein*" (MCP) proved mutations (not combined with other gene defects) may be *safe* for kidney donation") is misleading: Does it refer to an eventual kidney *donor* or *recipient*?	- Safety can be expected for both sides.

13)	16] Tables & Figures: They're all *clear* & *easy* to read. Do they have the *respective approvals* to be included in the manuscript? All of them are adapted from other publications.	**"Open access"**: All articles published under this title "Open Access" applies the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial.
14)	17] References: OK. Pl add the *clinical trials* supp: EZ FDA approval in aHUS.	*102. Loirat C, Babu S, Furman R, Sheerin N, Cohen D, Gaber O, et al. Eculizumab Efficacy and Safety in Patients With Atypical Hemolytic Uremic Syndrome (aHUS) Resistant to Plasma Exchange/Infusion [poster]. Presented at the 16th Congress of European Hematology Association (EHA), 2011. London, UK.* *103. Loirat C, Muus P, Legendre C, Douglas K, Hourmant M, Delmas Y, et al. A Phase II Study of Eculizumab in Patients With Atypical Hemolytic Uremic Syndrome Receiving Chronic Plasma Exchange/Infusion [poster].. Presented at the 16th Congress of European Hematology Association (EHA), 2011. London, UK.*

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No	Author (**03727922**)	Response
	I believe the manuscript is very *interesting and illustrative*. However, I don ŕ particularly like this kind of review because there wasn no methodology, which I would recommend to evaluate the inclusion. Furthermore, I recomend include the study objective, benefits, what the real news of this manuscript. I suggest setting the pattern for the figures and tables, making news table and not using from others adapted articles.	❖ ***Methodology***: In view of the lack of prospective controlled trials concerned with complement-mediated diseases post kidney transplant, we tried in this review to shed the light on the most recent experts' opinions, as regard the best tools of management of these devastating diseases. (included). ❖ Tables and figures: -Not all the tables and figures are vulnerable for amendment, as-for example- tissue biopsy histopathological findings, gene aberrations- concerned

		tables, as well as extrarenal disease manifestations, cannot be amended. ❖ However, figure 4 & 5, as well as tables: 5, 6, 7, 8 and 9 have been amended.

-THANK YOU ALL.