ANSWERING REVIEWERS

REVIEWER 1 (ID 05458182)

We thank the reviewer for the kind comments.

REVIEWER 2 (ID 03538272)

1) A Table summarizing individuals or symptoms that should be considered as indications for testing for celiac disease will benefit the initial section.

Response: Thanks for the suggestion. A new Table (Table 1) has been added, which includes the main symptoms which might prompt a diagnostic workup for celiac disease

2) A figure going through a suggested diagnostic algorithm for patients with suspected celiac disease and when the major tests would be used would be valuable for clinicians.

Response: A new Figure (Figure 2) has been added to address this point.

3) Table 9: there needs to be a space between “GFD” and “which”

Response: Thank you very much, the error has been corrected.

REVIEWER 3 (ID 03544596)

1) Tables are complex, tables should be simple and understandable.

Response: We simplified the text contained in the Tables. To btain this aim we performed both a language check to generate simpler sentences and divided the longest remaining paragraph in multiple sentences.

2): There are minor language errors.

Response: A language revision has been performed. All errors should have been fixed.

REVIEWER 4 (ID 03307766)

1) “Celiac disease (CD) is an immune-mediated REACTION to gluten characterized….”. CD is a well-)defined immune-mediated DISEASE, not just a “reaction”.

RESPONSE: We agree with the reviewer that a better term can be used. We adopted the Oslo definition for CD. The text was modified as follows: “Celiac disease (CD) is an immune-mediated reaction to gluten characterised by an inflammatory injury to the small bowel in genetically predisposed subjectsas a result of an inappropriate T cell-mediated immune response” and the original reference was removed.

2) “CD’s epidemiology…”. I wouldn’t use the genitive.

RESPONSE: Thanks for the suggestion, we modified the text.

3) What the authors mean with the expression “in the age of gluten-related disorders”: this is not clear.

RESPONSE: We removed the unclear expression.

4) The authors correctly suggest that the correct and timely diagnosis of CD is still a problem; however, the cited references (n.3: 2007; n.4: 2016; n.5: 2009; n.6: 2009) are not recent and I do not think they can support this concept as an ongoing issue. Therefore, I suggest the authors to change all these references with more recent and appropriate ones. Moreover, by doing that, the authors should emphasize the concept that such a problem is present everywhere but could especially affect developing countries and may have a higher impact in children (see some very recent papers where this issue is clearly discussed across different geographical/economical setting: World J Gastroenterol. May 21, 2021; 27(19): 2251-2256, doi: 10.3748/wjg.v27.i19.2251; Eur J Pediatr. 2021 Jun;180(6):1941-1946. doi: 10.1007/s00431-021-03974-8; PLoS One. 2020 Jan 2;15(1):e0226546. doi: 10.1371/journal.pone.0226546; J PediatrGastroenterolNutr. 2019 Oct;69(4):443-448. doi: 10.1097/MPG.0000000000002424; Dig Liver Dis. 2021 Apr;53(4):504-505. doi: 10.1016/j.dld.2021.01.008). These articles may also provide insightful suggestions for the discussion and perspective section.

RESPONSE: Thanks for your suggestion. The old references were removed and the new one added, according to the reviewer’s preference. INTRODUCTION: “ However, CD remains largely underdiagnosed in developing countries and has a higher impact on children[3,4]. Simultaneously, the misdiagnosis of CD is becoming an emergentproblem worldwide. [5].”; DISCUSSION: “Especially in Russia and Central Asia, the prevalence of CD is very likely to be underestimated due to poor disease awareness among physicians and/or patients, limited access to diagnostic resources, inappropriate use or interpretation of the serological tests, absence of standardised diagnostic and endoscopic protocols, and insufficient expertise in histopathological interpretation [3]”;” However, in an era during which the COVID-19 pandemic has caused a staggering drop in new CD diagnoses even in industrialised countries[81], ESPGHAN released the advice to lower the TGA-IgA threshold for diagnosing CD without biopsy [52]”; “Nowadays, significant diagnostic delays can still occur in a minority of Central European children[82], with socioeconomically deprived children being more likely to be underdiagnosed despite improved and easily available serological testing [4]”.

5) “…avoid life-threatening complications deriving from unrecognised CD…”. I think the authors should define/explain what these complications are or may be. Of course, this sentence should be supported by additional and appropriate references. In general, this paragraph should be supported by references, that are not present at all.

RESPONSE: Thanks for your suggestion. We modified the sentence as follows: “An evidence-based approach is needed to optimise diagnostic accuracy to avoid life-threatening complications (including small bowel carcinoma and lymphoma)[6]resulting from unrecognised CD on the one hand, and unnecessary cost burden and impact on the quality of life due to incorrect prescription of a life-long gluten-free diet (GFD) on the other hand. Simultaneously, follow-up of patients with CD who are on a GFD is of critical importance to assess the responsiveness to the GFD, detect complicated CD, find associated autoimmune diseases, and identify metabolic alterations induced by the GFD[7]”.We also added the appropriate references.

6) The authors define this manuscript as “systematic review”. The authors should provide a figure including the PRISMA flow diagram, in addition to describe in detail all the phases in the text. The literature search is the first phase and, therefore, it should be a part of a more comprehensive Materials and Methods section, including the specific aims, protocol, search strategy and data extraction. In part, this information is already present, but needs to be completed and included in a well-structured materials and methods section.

RESPONSE: We added the missing information and provided a PRISMA flow diagram in Figure 1. We also modified the pertinent paragraph as follows “The primary aim of this review was to identify the most recent national and international guidelines for CD by the means of a systematic review, and to compare their main recommendation.

We performed a database search on PubMed and selected papers published between January 2010 and January 2021 in the English language. PubMed was last accessed on 1 March 2021. The following keywords and terms were used:

1) Coeliac Diseaseor Celiac Disease

2) Guideline.

3) Management.

The following string was used: (("coeliac disease"[All Fields] OR "celiac disease"[MeSH Terms] OR ("celiac"[All Fields] AND "disease"[All Fields]) OR "celiac disease"[All Fields] OR ("coeliac disease"[All Fields] OR "celiac disease"[MeSH Terms] OR ("celiac"[All Fields] AND "disease"[All Fields]) OR "celiac disease"[All Fields])) AND ("guideline"[Publication Type] OR "guidelines as topic"[MeSH Terms] OR "guideline"[All Fields] OR ("manage"[All Fields] OR "managed"[All Fields] OR "managements"[All Fields] OR "managements"[All Fields] OR "manager"[All Fields] OR "manager s"[All Fields] OR "managers"[All Fields] OR "manages"[All Fields] OR "managing"[All Fields] OR "management"[All Fields] OR "organization and administration"[MeSH Terms] OR ("organization"[All Fields] AND "administration"[All Fields]) OR "organization and administration"[All Fields] OR "management"[All Fields] OR "disease management"[MeSH Terms] OR ("disease"[All Fields] AND "management"[All Fields]) OR "disease management"[All Fields])))

A total of415 papers were identifiedwith no duplicates, and, as a first step, no papers were excluded for other reasons (PRISMA flow diagram reported in Figure 1).However, twenty-one records were unavailable, leaving 396 papers for further evaluation. As a second step, we excluded papers that were not pertinent to any of the following criteria: 1) clinical guidelines related to diagnosis and management of CD; 2) clinical guidelines published by governmental agencies and scientific associations. We included only the last version of the guidelines, excluding the previous updated versions.

According to the selection criteria,out of the 396 results of PubMed research assessed for eligibility, seven guidelines were finally included in this analysis…”

7) Probably, the authors should also introduce and explain here their analysis strategy, according to the structure that they gave to the results section, in my opinion).

RESPONSE: We agree with the reviewer. WE added the following specification: “The recommendations provided by each selected guideline were systematically explored and classified into five categories: patients to be tested for CD, diagnostic tests (serology, duodenal biopsy, genetic test, no-biopsy diagnosis),

potential/silent/seronegative CD, refractory/complicated CD, and follow-up. These categories represent the most discussed topics of CD. “

8) I do not agree with the fact that the authors merged results and discussion, because each subsection of the results includes both aspects, actually. The authors should completely revise this organization and separate the results from the discussion .In the results, they should present their interesting and “objective” findings summarized in the tables and, therefore, these tables should drive the manuscript at this level. - For instance, in section 1: the results are the description and comparison of the guidelines recommendations according to different symptoms (gastrointestinal vs. extra-gastrointestinal, inclusion of specific symptoms, etc.). Then, the authors can arrange a different section (discussion) with the same substructure by discussing and commenting the different points. This manuscript organization would be much more appropriate for a systematic review, which aims to be objective and not narrative. CONCLUSION - the conclusion should not include any references (or very few). Here, the authors should provide and summarize their take-home and practical messages very clearly. REFERENCES - to be critically revised and, then, completed and updated. Indeed, out of around 70 references used after the search strategy, only 15-16 were published after 2015; I think the authors may have found more recent and original references for many aspects (e.g. HLA testing, refractory CD).

RESPONSE: Thank you very much for these comprehensive and useful suggestions. We tried to address this point combining scientific soundness and readability. We critically revised and modified the references according to the reviewer’s suggestions. After our revision 10 papers published after 2017 were added, including original papers and reviews. It should be noted that most guidelines selected according to the protocol were published after 2015, and all evidence-based guidelines are backward-looking by nature. AS such, most of the supporting evidence dated before 2015. The following references were added:

3 Poddighe D, Abdukhakimova D. Celiac Disease in Asia beyond the Middle East and Indian subcontinent: Epidemiological burden and diagnostic barriers. World J Gastroenterol. 2021 21;27:2251-2256. [DOI: 10.3748/wjg.v27.i19.2251]

4 Whitburn J, Rao SR, Paul SP, Sandhu BK. Diagnosis of celiac disease is being missed in over 80% of children particularly in those from socioeconomically deprived backgrounds. Eur J Pediatr. 2021;180:1941-1946. [DOI: 10.1007/s00431-021-03974-8]

6 Biagi F, Schiepatti A, Maiorano G, Fraternale G, Agazzi S, Zingone F, Ciacci C, Volta U, Caio G, Tortora R, Klersy C, Corazza GR. Risk of complications in coeliac patients depends on age at diagnosis and type of clinical presentation. Dig Liver Dis. 2018;50:549-552.. [DOI: 10.1016/j.dld.2017.12.001.]

7 D'Avino P, Serena G, Kenyon V, Fasano A. An updated overview on celiac disease: from immuno-pathogenesis and immuno-genetics to therapeutic implications. Expert Rev Clin Immunol. 2021;17:269-284. [DOI: 10.1080/1744666X.2021.1880320]

44 Poddighe D, Kushugulova A. Salivary Microbiome in Pediatric and Adult Celiac Disease. Front Cell Infect Microbiol. 2021;11:625162.[DOI: 10.3389/fcimb.2021.625162]

45 Abdukhakimova D, Dossybayeva K, Poddighe D. Fecal and Duodenal Microbiota in Pediatric Celiac Disease.. Front Pediatr. 2021;9:652208. [DOI: 10.3389/fped.2021.652208]

50 Poddighe D, Rebuffi C, Silvestri AD, Capittini C. Carrier frequency of HLA-DQB1*02 allele in patients affected with celiac disease: A systematic review assessing the potential rationale of a targeted allelic

genotyping as a first-line screening. World J Gastroenterol. 2020;26:1365–1381.[DOI: 10.3748/wjg.v26.i12.1365].

51 De Silvestri A, Capittini C, Poddighe D, Valsecchi C, Marseglia G, Tagliacarne SC, Scotti V, Rebuffi C, Pasi A, Martinetti M, Tinelli C. HLA-DQ genetics in children with celiac disease: a meta-analysis suggesting a two-step genetic screening procedure starting with HLA-DQ β chains. Pediatr Res. 2018;83:564-572. [DOI: 10.1038/pr.2017.307]

81 Valitutti F, Troncone R, Pisano P, Ciacci C; Campania Coeliac Disease Network. Where have all the other coeliacs gone in 2020? Road for a 2021 catch-up with missed diagnoses. Dig Liver Dis. 2021;53:504-505.[DOI: 10.1016/j.dld.2021.01.008]

82 Riznik P, De Leo L, Dolinsek J, Gyimesi J, Klemenak M, Koletzko B, Koletzko S, Korponay-Szabó IR, Krencnik T, Not T, Palcevski G, Sblattero D, Werkstetter KJ, Dolinsek J. Clinical Presentation in Children With Coeliac Disease in Central EuropeJ Pediatr Gastroenterol Nutr. 2021;72:546-551. [DOI: 10.1097/MPG.0000000000003015]

Regarding the structure of the paper, the reviewer is absolutely right. We adopted a a similar way of presentation in other papers as well. In the peculiar case of this paper (given the wide range of treated topics), however, proceeding in such a way would result in a first part of the paper composed by 10 consecutive tables with few supporting text, followed by a long discussion without figures or tables, and a final result of a 20-paragraph paper. We feared that a similar structure would have resulted in a loss of readability (especially for readers not fully proficient in celiac disease) despite being the most correct one. We are open to any Editor suggestion about this point, as we have no a priori preclusions.