CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Celiac Disease and Increased Risk of Pneumococcal Infection: A Systematic Review and Meta-Analysis

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ABSTRACT

BACKGROUND: Celiac disease has been associated with hyposplenism, and multiple case reports link celiac disease and pneumococcal infections; however, increased risk of pneumococcal infection in celiac disease has not been confirmed. The purpose of this study was to conduct a systematic review to determine the risk of pneumococcal infections in celiac disease.

METHODS: Relevant studies were identified using electronic bibliographic searches of PubMed, OVID, Medline, and EMBASE (1980 to February 2017) and reviewing abstracts from major conferences in gastroenterology. Using number of events in celiac patients and referent patients, we calculated a summary relative risk of pneumococcal infections. All analyses were conducted in Comprehensive Meta-Analysis software using random-effects assumptions.

RESULTS: Of a total of 156 articles, 3, representing 3 large databases (the Swedish National Inpatient Register; the Oxford Record Linkage Study; and the English National Hospital Episode Statistics) were included. Each compared patients with celiac disease and confirmed pneumococcal infection to a specific reference group: inpatients and/or the general population. Overall, the odds of pneumococcal infection were higher among hospitalized celiac patients compared with controls (odds ratio 1.66; 95% confidence interval 1.43-1.92). There was no evidence of heterogeneity ($Q[1] = 1.17$, $P = .56$, $I^2 = 0\%$).

CONCLUSIONS: Celiac disease is associated with an increased risk of pneumococcal infection. Preventive pneumococcal vaccination should be considered for those with celiac disease, with special attention to those aged 15-64 years who have not received the scheduled pneumococcal vaccination series as a child.

 • The American Journal of Medicine (2018) 131, 83–89

KEYWORDS: Celiac disease; Hyposplenism; Infection; Pneumococcus; Splenic atrophy

Funding: None.

Conflict of Interest: None.

Authorship: Author contributions are as follows. MS: conception of the work, acquisition and interpretation of the data, lead author. LAJS-S: data analysis, author. YR-N: conceptualization, analysis of data, author. SM: contributing author, data analysis, critical review of the intellectual content. JFL: major contributing author, interpretation of data, critical revision of manuscript. PHRG: supervising author, critical revision of the data and intellectual content. All authors approve the final submitted draft.

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0002-9343/$ - see front matter
https://doi.org/10.1016/j.amjmed.2017.07.021

INTRODUCTION

Celiac disease is an immune-mediated multisystem disorder affecting primarily the small bowel in response to gluten ingestion. Among the manifestations of celiac disease, an increased risk for serious infections has been documented,[1-4] though guidance for vaccination in these vulnerable patients is not well established.

Immune system dysfunction in this patient population has largely been attributed to hyposplenism and resultant B-cell and neutrophil impairment.[5-7] The incidence of hyposplenism in patients with celiac disease, evaluated by presence of Howell-Jolly bodies, pitted red blood cells, or nucleotide scans, has been estimated from 19% to 80%, and the risk may be higher when celiac disease is associated with other autoimmune diseases.[8] The cause of this association is not well understood.

Asplenia and hyposplenism are known risk factors for overwhelming infection by encapsulated bacteria. Because of this, the Infectious Disease Society of America recommends that conditions associated with splenic function impairment, such as sickle cell anemia, be considered indications for immunization against encapsulated organisms. The British Society of Gastroenterology updated its 1996 guidelines for celiac disease management in 2014 to include the recommendation for vaccination against pneumococcal disease (grade C recommendation).[9] There is no similar guideline for vaccination against pneumococcus in celiac disease in the United States.[10] Therefore, the purpose of this study was to conduct a systematic review of the available scientific literature documenting the risk of pneumococcal infections.

CLINICAL SIGNIFICANCE

- Celiac disease is associated with hyposplenism and splenic atrophy, which are known risk factors for infection by encapsulated bacteria, such as *Streptococcus pneumoniae*.
- Patients with celiac disease are at increased risk for pneumococcal infection, particularly those who were not vaccinated in childhood or as older adults.
- Preventive pneumococcal vaccination should be considered for those with celiac disease, especially those between the ages 15 and 64 years who may not have received pneumococcal vaccination.

METHODS

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[11]

Eligibility Criteria

To be included in the systematic review, cohort studies were required to sample patients with celiac disease according to International Classification of Diseases codes, or equivalent codes in other revisions of the International Classification of Diseases for celiac disease, and medically confirmed pneumococcal infection (including pneumonia, meningitis, bacteremia), compared with controls. Studies of patients with respiratory infections without confirmed pneumococcus were excluded.

Information Sources and Search

Studies were retrieved from 3 sources: (1) bibliographic database searches; (2) conference abstracts; and (3) review of reference sections of relevant articles. First, 3 electronic bibliographic databases (PubMed, OVID Medline, and EMBASE) were searched for eligible studies using the following search terms: "celiac disease," "coeliac disease" and "hyposplenic," "hyposplenism," "infection," "pneumococcal infections," "pneumococcal pneumonia," "pneumococcal meningitis," or "*Streptococcus pneumoniae*." Searches were restricted to studies published between January 1, 1980 and February 28, 2017 because this timeframe includes periods before and after pneumococcal vaccination availability in the early 1990s. In addition, although celiac disease was described well before the 1980s, the 1990s had more reliable and widely agreed-upon diagnostic tools to define celiac disease.[12] No language restrictions were applied. All searches were conducted by a medical librarian at Rhode Island Hospital. Second, abstracts accepted for the 2006-2015 annual meetings of Digestive Disease Week and the American College of Gastroenterology were reviewed. Finally, reference sections of relevant articles (including editorials and narrative reviews) were examined.

All studies were evaluated for possible inclusion by 2 of the investigators (MS and YRN). Of the 81 studies assessed for eligibility, 53 studies were excluded because of irrelevance to the clinical question (infection risk not assessed, no celiac disease identified, and studies examining infections as a risk factor for later development of celiac disease). Fifteen studies were excluded because of non-pneumococcal infections or unidentified organisms. Seven case reports or case series regarding pneumococcal infections in patients with celiac disease included fewer than 3 subjects and were therefore excluded. Three studies were excluded because patients with celiac disease were subject to other causes of immunosuppression (human immunodeficiency virus/acquired immunodeficiency syndrome and anti–tumor necrosis factor therapy).[13-15] One additional study met inclusion criteria but included duplicated data from Sweden[4] and thus was only reported as part of the systematic review.

Data Collection

Two authors of this study (MS and YRN) independently extracted patient characteristics (specifically patient location, sample size, age, and sex) and outcome data. The authors of the studies that met the inclusion criteria were contacted to retrieve pertinent data that were not available in the article.

Effect Size Calculations

The number of patients with pneumococcal infections and the sample size were extracted from each study. If a study did not provide the patients or sample size, this information was requested from the authors.

Statistical Analyses

The number of pneumococcal infections in celiac patients and referent patients was used to calculate the log odds ratio and the corresponding standard error, which was then converted back to an odds ratio.[16] The weighted summary statistic was computed using random effects procedures. The homogeneity statistic, Q, was calculated; a significant Q indicates a lack of homogeneity and an inference of heterogeneity. The I^2 index and the corresponding 95% confidence intervals were also calculated to assess the observed dispersion.[17-19] The I^2 index ranges from 0 to 100%, with 25%, 50%, and 75%, considered low, moderate, and high levels of observed variance reflecting true differences in effect size.[20] All analyses were conducted in Comprehensive Meta-Analysis.[21]

RESULTS

Study Selection

A total of 156 potentially relevant articles were reviewed on the basis of our inclusion criteria. Three articles met the inclusion criteria for the systematic review (**Figure 1**). The cohorts included Sweden (Swedish National Inpatient Register; SNIR);[1] Oxford, United Kingdom (UK) (Oxford Record Linkage Study; ORLS);[2] and England, UK (English National Hospital Episode Statistics; EHES),[2] as well as data collected from Swedish pathology departments (**Table**). Data from the Swedish pathology departments were also reported as part of the SNIR, and therefore we opted to include the article with the most comprehensive data (ie, SNIR) to use in the pooled analyses, to avoid violating the assumption of independence. Each database involved patients with celiac disease and confirmed pneumococcal infection compared with a specific reference group: patient population (referred to as "patients") and/or the general population.

Study Outcomes for All Ages

The Sweden (SNIR and Swedish pathology department), Oxford, and England cohorts showed an increased risk of pneumococcal infection when compared with controls (**Figure 2**). The data for all cohorts were adjusted for socioeconomic index and diabetes mellitus (SNIR); level of education, socioeconomic status, and country of birth (Swedish pathology department); and sex, age, time period in a single calendar year, and district of residence (Oxford and England).

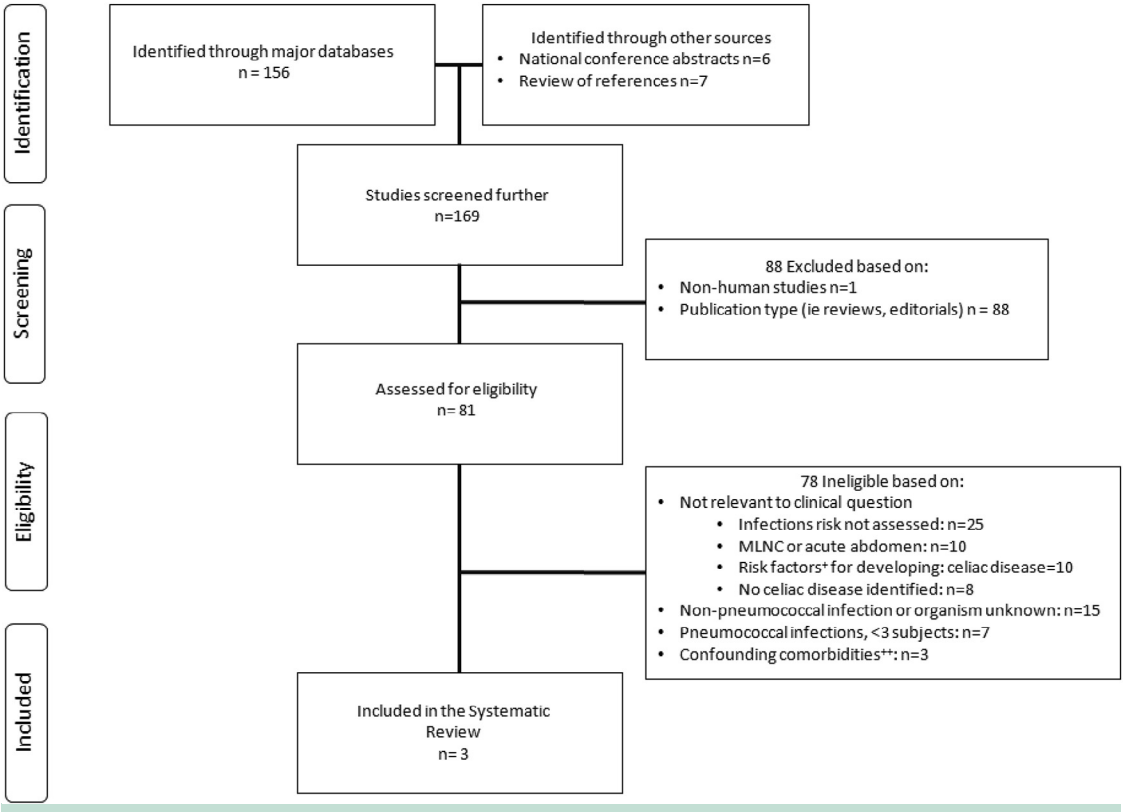

Figure 1 Study search and selection flow diagram. MLNC = mesenteric lymph node cavitation. +Studies examining association between prediagnosis infections and later development of celiac disease. ++Such as human immunodeficiency virus/acquired immunodeficiency syndrome or anti–tumor necrosis factor therapy.

Table Overview of the Study and Patient Characteristics

Study	Location	Population	No. of Patients with Celiac Disease	No. of Reference Individuals	% Adults	% Female
Ludvigsson	Sweden	Patients	15,325	14,494	38	19
Ludvigsson	Sweden	General	14,250	69,357	35	59
Thomas	Oxford	Patients	2044	592,174	58	NR
Thomas	England	Patients	18,928	NR	64	NR
Tjernberg	Sweden	Outpatients	29,012	144,257	59	62

"% Adults" is the proportion of the population aged ≥16 years for the Sweden cohort,[1] 15-64 years for the Oxford and England cohorts,[2] and ≥20 years in the other Sweden cohort.[46] NR = not reported.

Risk of Infection by Age of Patients

Each group was further reported by age (**Figure 3**). In Sweden, celiac disease patients aged ≥16 years were at a high risk of pneumococcal infection (hazard ratio [HR] 2.80, 95% confidence interval [CI] 1.30-6.30). The English cohort showed that the greatest risk was between ages 15 and 64 years, with the lowest, but still apparent, risk after age 64 (rate ratio [RR] 1.38, 95% CI 1.10-1.72 vs RR 2.07, 95% CI 1.57-2.68). The Oxford database did not stratify by age, but overall patients with celiac disease doubled their risk for pneumococcal infection compared with referent patients (RR 2.06, 95% CI 1.27-3.15), which is higher than that risk when combining all ages in the English study.

Risk of Infection Compared with the General Population

Only the Sweden cohorts compared the risk of pneumococcal infection in celiac disease with that of the general population (**Figures 2 and 3**). The risk of pneumococcal infection was more pronounced when celiac disease patients were compared with reference individuals from the general population (HR 3.90, 95% CI 2.20-7.00), and the increased risk of pneumococcal infection remained when examining biopsy-proven celiac disease from Sweden pathology reports (HR 1.46, 95% CI 1.05-2.03). When age was considered, the risk of pneumococcal infection was slightly higher in people above age 16 years than when compared with that of all ages

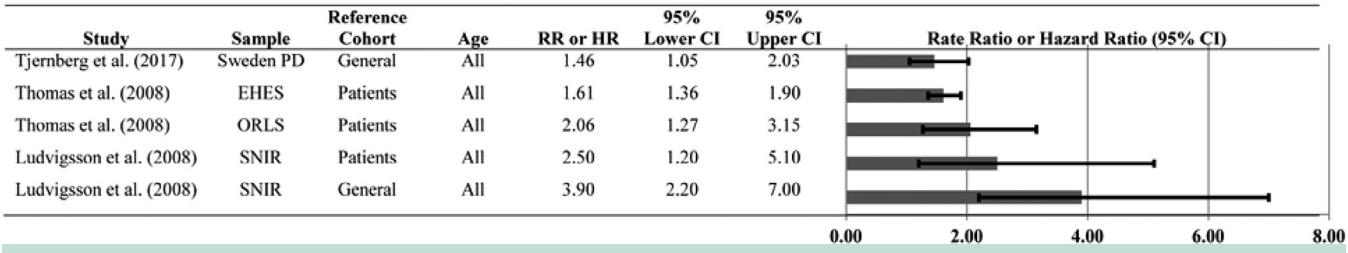

Figure 2 Risk of pneumococcal infection in patients with celiac disease compared with inpatient references or the general population for all ages. CI = confidence interval; EHES = English National Hospital Episode Statistics; HR = hazard ratio estimated using internally stratified Cox regression; ORLS = Oxford Record Linkage Study; PD = pathology department; RR = rate ratio; SNIR = Swedish National Inpatient Register.

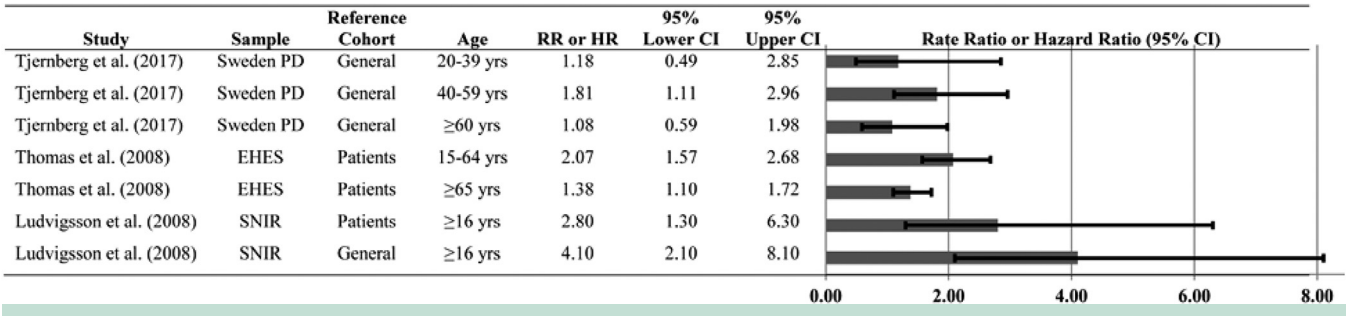

Figure 3 Risk of pneumococcal infection in patients with celiac disease compared with inpatient references or the general population, by age group. CI = confidence interval; EHES = English National Hospital Episode Statistics; HR = hazard ratio estimated using internally stratified Cox regression; ORLS = Oxford Record Linkage Study; PD = pathology department; RR = rate ratio; SNIR = Swedish National Inpatient Register.

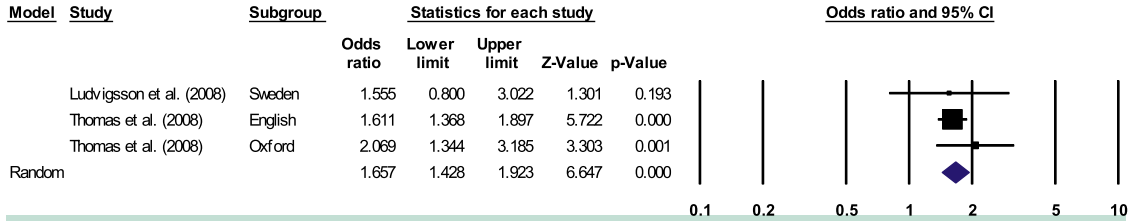

Figure 4 Overall risk of pneumococcal infection in patients with celiac disease compared with inpatient references. The overall effect size is indicated by a blue diamond. Odds ratios were calculated according to data provided by the authors. CI = confidence interval.

(HR 4.10, 95% CI 2.10-8.10 vs HR 3.90, 95% CI 2.20-7.00, respectively). Children (age <15 years) were still at increased risk for pneumococcal infection, but much less so than if they were older than 15 years (HR 3.40, 95% CI 1.10-10.60). Biopsy-proven celiac disease from Sweden pathology reports confirmed these findings, showing that the risk of pneumococcal infections was higher between ages 40 and 59 years (HR 1.81, 95% CI 1.11-2.96) and lower for patients aged 20-39 years (HR 1.18, 95% CI 0.49-2.85) or older than 60 years (HR 1.08, 95% CI 0.59-1.98).

Summary Effects

The data from the 3 independent cohorts (SNIR, ORLS, and EHES) were pooled, with an overall odds ratio for pneumococcal infection in patients with celiac disease, compared with inpatient references, of 1.66 (95% CI 1.43-1.92) (**Figure 4**). There was no evidence of heterogeneity ($Q[1] = 1.17$, $P = .56$, $I^2 = 0\%$).

DISCUSSION

Our study is the first systematic review and meta-analysis to determine the risk of pneumococcal infection in patients with celiac disease. Only European data were available in the literature, including 3 large regional databases (England, Oxford, both in the UK, and Sweden) with 2 referent groups (patient and general population). Overall, the odds of pneumococcal infection in people with celiac disease is approximately double that of controls.

Although both the English and Oxford populations showed an increase risk of pneumococcal infection in celiac disease, this was higher in the Oxford database (RR 2.06 vs RR 1.61). The Oxford study included data from the period 1963-1993, whereas the English study accounted for data from 1998-2003, a time when the pneumococcal vaccine was widely available. Furthermore, when the English population was analyzed by age, the risk for pneumococcal infection was less in ages >65 years. This is surprising because one would assume that this is a more vulnerable subset; however, after 1990, 29% of people in the UK that were aged ≥65 years were receiving pneumococcal vaccination, whereas before 1990, vaccination was unavailable.[22] These results advocate that not only does celiac disease increase the risk for pneumococcal infection, but prophylactic pneumococcal vaccination may be preventative.

Three major studies in the UK, Sweden, and Italy found that celiac disease is associated with greater mortality from respiratory infections and sepsis.[3,4,23] Interestingly, another UK study further evaluated the risk of respiratory infections after 1998, when pneumococcal vaccination was widely available, and found no significant increase risk of respiratory related deaths.[24] Recently a large retrospective cohort in the UK identified unvaccinated patients with celiac disease to have an excess risk of community-acquired pneumonia not found in vaccinated patients with celiac disease.[25] Although this study did not confirm pneumococcal pneumonia, it is still recognized as the most common type of pneumonia. In 2014 the British Society of Gastroenterology updated its 1996 guidelines for celiac disease management to include vaccination against pneumococcal disease (grade C recommendation).[9] Despite recommendations from the UK, pneumococcal vaccination in those with celiac disease has been underappreciated. In 2001 only 14% of UK celiac patients were vaccinated over a 5-year span, which increased to only 16% by 2005.[26] In 2013 a retrospective audit found that only 19% of those with celiac disease and aged <65 years received vaccination.[27] In the US and Sweden no such guidelines for celiac patients are available or enforced, potentially missing a crucial opportunity to intervene and protect patients with celiac disease from morbidity and mortality.

Laboratory, radiographic studies, and numerous case reports since the 1970s have linked pneumococcal infection risk to functional hyposplenism and splenic atrophy.[28-30] Hyposplenism is common in patients with celiac disease, ranging from 19% to 80%. Recently it has been shown that more complicated and progressive celiac disease is associated with smaller splenic volume.[31] Despite these concerns, patients with celiac disease have been shown to have an appropriate immunologic response to the polyvalent pneumococcal vaccine.[32]

There have been multiple case reports of pneumococcal infection (or sepsis) in patients with celiac disease, including from within the United States.[28-30,33-35] Our meta-analysis would suggest that the recommendation for pneumococcal vaccination should be robust, with special attention to those aged 15-64 years. Our data show that this age group seems to be at the highest risk for pneumococcal infection in celiac disease. The lower, but still apparent, risk for infection in those aged <15 years may be because the conjugate pneumococcal vaccination (PCV7) was added to the childhood vaccination schedule in 2000, which was then replaced by the PCV13 to

include 13 more strains of pneumococcus in 2010.[36] This offers a level of protection that was not provided for patients diagnosed with celiac disease between the ages of 15 and 64 years, the latter age signifying the age for which the Centers for Disease Control and Prevention recommends pneumococcal vaccination in the elderly. Thus, for this vulnerable population that was not vaccinated as in childhood, we believe that pneumococcal vaccination is a safe and potentially lifesaving intervention.

In addition to prophylactic pneumococcal vaccination, physicians should recognize the signs of splenic dysfunction, including pitting red blood cells and Howell-Jolly bodies on peripheral smears; however, these tests have poor sensitivity for measuring splenic function. Radioactive uptake tests have been used as well but are expensive and not always clinically relevant.[37] Because most patients have a full blood count, the presence of thrombocytosis should alert the physician to the potential for hyposplenism and splenic atrophy.[38] Abdominal imaging could then be performed to assess for splenic size.[39,40] There have been conflicting studies about whether diet can help reverse existing splenic disease, perhaps distinguishing irreversible splenic atrophy from reversible splenic hypofunction.[37,41-43] Given the significance of splenic hypofunction and atrophy, and ways to screen for this in celiac disease, vaccination against pneumococcal infection seems to be a safe and productive way to protect patients in the future.

Although we believe the results of this review are paramount to the management of patients with celiac disease, we recognize the study's limitations. First, our comprehensive literature search indicated that only 2 articles representing 3 samples with a total of 50,547 celiac disease patients were available for our meta-analysis. Despite the limited number of studies available for meta-analysis, meta-analytic scholars maintain that 2 studies are sufficient to conduct a meta-analysis and will provide a more precise estimate of the true effect than either study alone.[44,45] Furthermore, in the absence of a meta-analytic review, researchers will inevitably summarize the data, "which will invariably be less accurate and more idiosyncratic" than meta-analytic estimates.[44] Second, we were unable to conduct additional analyses to determine predictors (eg, proportion of women, geographic location) of the association between celiac disease and pneumococci. Third, we acknowledge that there are limited data regarding vaccination status worldwide. If a proportion of patients with celiac disease in the 2 studies[1,2] were already vaccinated, our meta-analysis may have underestimated the risk of pneumococcal infections in celiac disease. Finally, our data provide insight into the average patient with celiac disease; specifically, we were unable to stratify the risk of pneumococcal infection in patients with poorly controlled celiac disease according to symptoms, titers, or the presence of villous atrophy.

CONCLUSION

This systematic review and meta-analysis showed that celiac disease is associated with pneumococcal infection. Vaccination against pneumococcal infection in celiac disease should be strongly recommended for all age groups, with an emphasis for those who were not vaccinated as a child.

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