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

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1. Malorie Simons, MD- conception of the work, acquisition and interpretation of the data, lead author. Author approves this final submitted draft.
2. Lori A. J. Scott-Sheldon, PhD- data analysis, author. Author approves this final submitted draft.
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Highlights

- 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 to 64 who may have not received pneumococcal vaccination.

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 manuscripts, 3, representing three large databases including 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 to controls (odds ratio= 1.66; CI 95% 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 ages 15 to 64 who have not received the scheduled pneumococcal vaccination series as a child.

Keywords: celiac disease; pneumococcus; infection; splenic atrophy; hyposplenism

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). Incidence of hyposplenism in patients with celiac disease, evaluated by presence of Howell-Jowell bodies, pitted red blood cells, or nucleotide scans has been estimated from 19-80%, 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.

Methods

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

Eligibility Criteria

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

Information Sources and Search

Studies were retrieved from three sources: (1) bibliographic database searches, (2) conference abstracts, and (3) review of reference sections of relevant papers. First, three 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 as this timeframe includes the pre and post-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 to 2015 annual meetings of *Digestive Disease Week* and the *American College of Gastroenterology* were reviewed. Finally, reference sections of relevant manuscripts (including editorials and narrative reviews) were examined.

All studies were evaluated for possible inclusion by two of the investigators (MS and YRN). Of the 81 studies assessed for eligibility, 53 studies were excluded due to 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 as patients with celiac disease were subject to other causes of immunosuppression (HIV/AIDS and anti-TNF 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, 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 paper.

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 were 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 manuscripts were reviewed based on our inclusion criteria. Three manuscripts 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 . Data from the Swedish pathology departments were also reported as part of the SNIR and therefore, we opted to include the manuscript with the most comprehensive data (i.e., 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 to 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 to 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).

Risk of Infection by Age of Patients

Each group was further reported by age (Figure 3). In Sweden, celiac disease patients 16 years of age or older were at a high risk of pneumococcal infection (HR = 2.80, 95% CI = 1.30, 6.30). The English cohort showed the greatest risk was between ages 15 and 64, with the lowest, but still apparent, risk after age 64 (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 to 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 to the General Population

Only the Sweden cohorts compared the risk of pneumococcal infection in celiac disease to 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 than when compared that of to all ages (HR = 4.10, 95% CI = 2.10, 8.10 vs. HR = 3.90, 95% CI = 2.20, 7.00, respectively). Children (less than age 15) 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 (HR = 1.81, 95% CI = 1.11, 2.96), and lower for patients 20 to 39 years of age (HR = 1.18, 95% CI = 0.49, 2.85) or older than age 60 (HR = 1.08, 95% CI = 0.59, 1.98).

Summary Effects

The data from the three independent cohorts (SNIR, ORLS, and EHES) were pooled with an overall odds ratio for pneumococcal infection in patients with celiac disease, compared to inpatient references, of 1.66 (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 three large regional databases (England, Oxford, both in the UK, and Sweden) with two 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 versus RR 1.61). The Oxford study included data from 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 over 65 years. This is surprising since one would assume that this is a more vulnerable subset; however, after 1990, 29% of people in the UK that were 65 and older were receiving pneumococcal vaccination whereas prior to 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 under age 65 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 19-80%. 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 US (28-30, 33-35). Our meta-analysis would suggest that the recommendation for pneumococcal vaccination should be robust, with special attention to those between ages 15 and 64. Our data show that this age group appears to be the highest risk for pneumococcal infection in celiac disease. The lower, but still apparent, risk for infection in those less 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 ages 15 to 64, the latter age signifying the age for which the CDC recommends pneumococcal vaccination in the elderly. Thus, for this vulnerable population that was not vaccinated as a child, we believe that pneumococcal vaccination is a safe and potentially life-saving 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 appears 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 two manuscripts representing three 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 two 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 (e.g., proportion of women, geographical 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 two 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 based upon 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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Figure 1. Study search and selection flow diagram.
MLNC = mesenteric lymph node cavitation; [+]Studies examining association between pre-diagnosis infections and later development of celiac disease; [++]Such as HIV/AIDS or anti-TNF therapy.

Figure 2. The Risk of Pneumococcal Infection in Patients with Celiac Disease Compared to Inpatient References or the General Population for All Ages

Note. EHES, English National Hospital Episode Statistics; ORLS, Oxford Record Linkage Study; SNIR, Swedish National Inpatient Register; RR, rate ratio; HR, hazard ratio estimated using internally stratified Cox regression; CI, confidence interval.

Figure 3. The Risk of Pneumococcal Infection in Patients with Celiac Disease Compared to Inpatient References or the General Population by Age Group

Note. EHES, English National Hospital Episode Statistics; ORLS, Oxford Record Linkage Study; SNIR, Swedish National Inpatient Register; RR, rate ratio; HR, hazard ratio estimated using internally stratified Cox regression; CI, confidence interval.

Figure 4. Overall Risk of Pneumococcal Infection in Patients with Celiac Disease Compared to Inpatient References†

Note. The overall effect size is indicated by a blue diamond. CI, confidence interval. †Odds ratios were calculated based on data provided by the authors.

Table 1. 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	2,044	592,174	58%	NR
Thomas	England	Patients	18,928	NR	64%	NR
Tjernberg	Sweden	Outpatients	29,012	144,257	59%	62%

Note. Adults is the proportion of the population ≥16 years of age for the Sweden cohort(1), 15 to 64 years of age for the Oxford and England cohorts (2), and ≥20 years of age in the Sweden cohort (46). NR, not reported.

Figure 1.

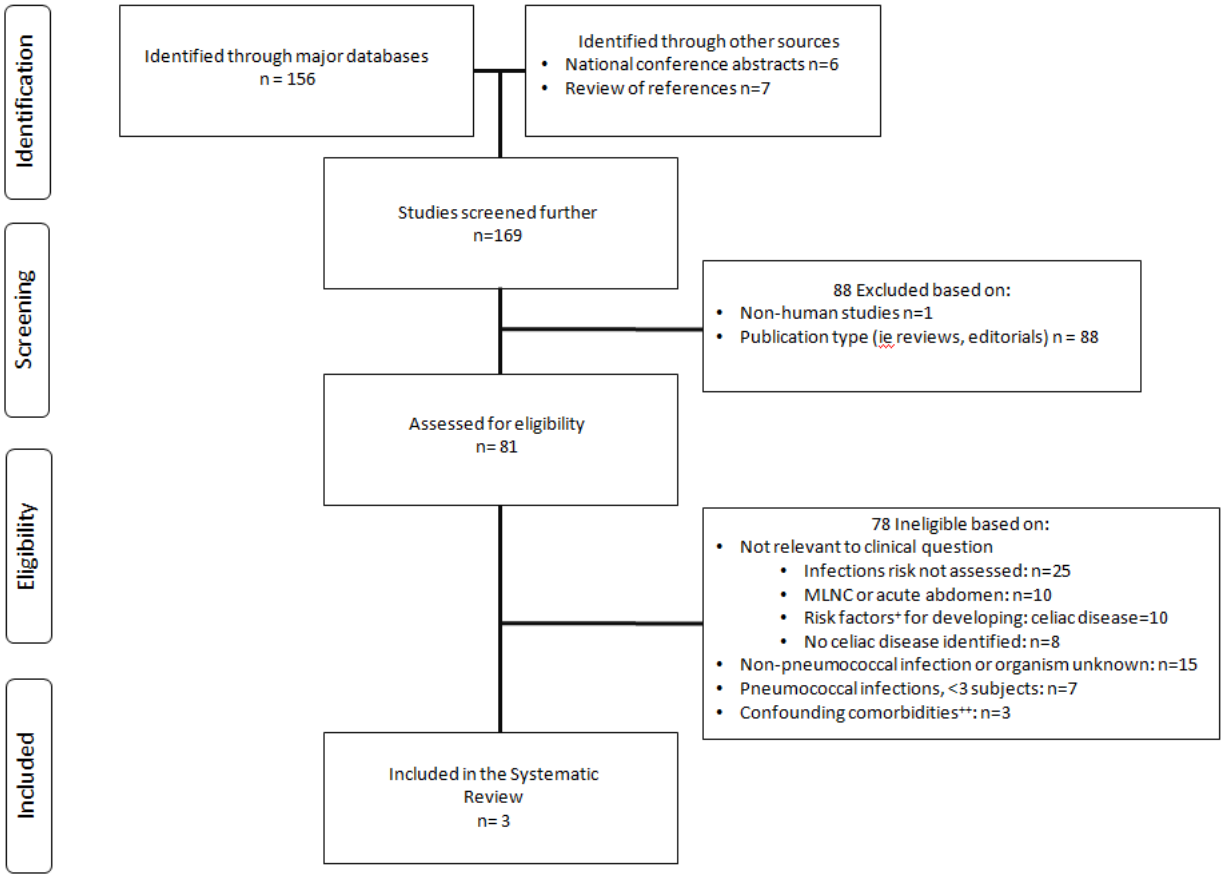
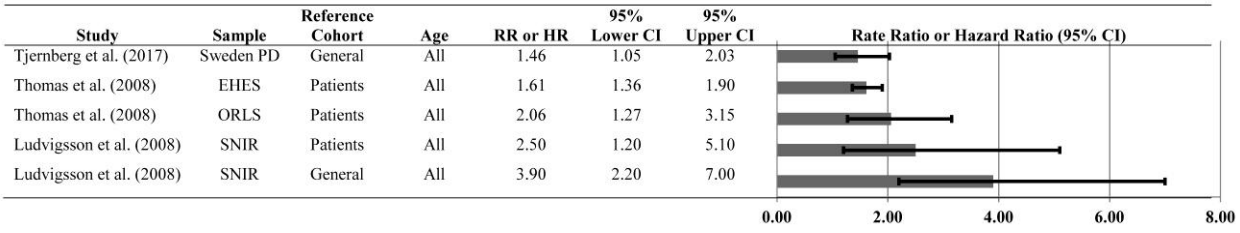


Figure 2.



Study	Sample	Reference Cohort	Age	RR or HR	95% Lower CI	95% Upper CI
Tjernberg et al. (2017)	Sweden PD	General	All	1.46	1.05	2.03
Thomas et al. (2008)	EHES	Patients	All	1.61	1.36	1.90
Thomas et al. (2008)	ORLS	Patients	All	2.06	1.27	3.15
Ludvigsson et al. (2008)	SNIR	Patients	All	2.50	1.20	5.10
Ludvigsson et al. (2008)	SNIR	General	All	3.90	2.20	7.00

Figure 3.

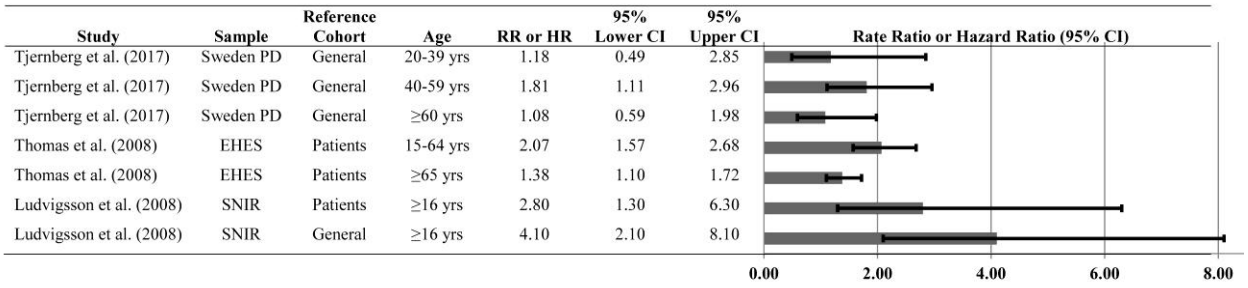


Figure 4.