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Mucosal healing and the risk of serious infections in patients with celiac disease

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Abstract

Background: Patients with celiac disease (CD) are at increased risk of certain infections, but it is unknown if mucosal healing influences this risk.

Methods: We collected data on 29,096 individuals with CD (equal to villous atrophy) through Sweden's 28 pathology departments undergoing biopsy 1969–2008. Through the Swedish Patient Register we obtained information on any infection and specifically sepsis, streptococcal infection, influenza, *Clostridium difficile*, herpes zoster and pneumococcal infection up until December 2009. We used Cox regression to calculate hazard ratios (HRs) for the risk of future diagnosis of infection according to mucosal healing on follow-up biopsy (persistent villous atrophy vs mucosal healing).

Results: Of 5598 CD individuals with no record of any infections before follow-up biopsy, 45% had persistent villous atrophy, 619 (24%) of them had a later infection, compared to 579 (19%) in those with mucosal healing ($p < 0.01$); the yearly incidence was 2.1% in both groups. Adjusting for age, sex, calendar period, time between biopsies and education, persistent villous atrophy was however not associated with later infection overall (HR = 0.99; 95% CI = 0.88–1.11) or with any of the specific infections.

Conclusions: In CD, mucosal healing does not influence the risk of serious infection requiring hospital-based medical attention.

Keywords

Celiac disease, infectious disease, epidemiology

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Key summary

- Celiac patients are at increased risk of several serious infections such as sepsis and pneumococci. It is, however, unknown how the risk of infections relates to mucosal healing.
- We show that mucosal healing, as compared to persistent villous atrophy, does not affect the risk of serious infections in celiac patients.

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Introduction

Celiac disease (CD) is a lifelong gastrointestinal disease with systemic features[1] and is characterized by small-intestinal inflammation and villous atrophy (VA).[2] Treatment consists of a gluten-free diet (GFD) aiming to decrease symptoms and heal the mucosa.

CD occurs in about 1%–2% of the general population of the Western world. Most earlier research has found an increased risk of mortality and morbidity in CD. Of particular note, CD increases the risk of certain infections[3] including severe disease such as sepsis,[4] and particularly sepsis due to *pneumococcal* infection.[4] The excess risk of pneumococcal infections has since been confirmed by British data,[5] and in many countries pneumococcal vaccination is recommended for CD patients.[6–8] In Sweden the general recommendation for pneumococcal vaccination in high-risk groups was introduced 1994; however, celiac patients have not been considered high-risk individuals in Sweden. Individuals with CD also appear to be at increased risk of a number of other infections such as influenza[9] and *Clostridium difficile*.[10]

Future risk of complications may be dependent on mucosal healing. Although overall mortality[11] is not associated with mucosal healing at follow-up biopsy, both lymphoproliferative cancer[12] and hip fracture[13] are more frequent in CD patients with persistent VA. We hypothesized that mucosal healing in CD influences the risk of subsequent infections.

In this study we linked population-based data on CD diagnosed according to biopsy records with disease codes for infections to examine if mucosal healing protects against future infections.

Methods

Study sample: Patients with CD undergoing repeated biopsy

In 2006–2008 we contacted all pathology departments in Sweden to obtain data on small-intestinal VA (Marsh III[14]). The biopsies had taken place between 1969 and 2008 (Table 1). For each biopsy sample we requested date and personal identity number[15] of the patient to allow for linkage to other registers. On average, each biopsy report was based on three tissue specimens.[16] A detailed review of the data collection has been published previously.[17] In Sweden, other causes of VA than CD are uncommon, and when we reviewed patient charts of 114 patients with a record of VA, 108 had CD (positive predictive value of 95% which is higher than having a physician-assigned diagnosis of CD in the Swedish Patient Register[18]).[17]

Out of an original sample of 29,096 CD patients, 9725 had undergone a follow-up biopsy. We restricted our study to those with a biopsy within the specified time frame of 0.5–5 years after the first diagnostic biopsy ($n = 7648$). Another 2050 were excluded since they had a record of hospital-diagnosed infectious disease prior to follow-up biopsy. Therefore, this study was ultimately based on 5598 CD patients without a history of infection who then underwent follow-up biopsy. Patients who had a modified Marsh histopathology score of 3 at follow-up biopsy were classified as having persistent VA, while those with a less severe score were classified as healed.

Table 1. Characteristics of patient cohort with celiac disease (CD) and follow-up biopsies without previously registered infectious diagnoses.

Characteristic	Mucosal healing, *n* (%)	Persistent villous atrophy, *n* (%)	*p* value (chi^2)
Total number	3066	2532	
Age at diagnosis of CD (years)			<0.01
0–19	1369 (45)	988 (39)	
20–39	670 (22)	386 (15)	
40–59	686 (22)	684 (27)	
≥60	341 (11)	474 (19)	
Male	1071 (35)	947 (37)	0.06
Female	1995 (65)	1585 (63)	
Interval between diagnosis and follow-up biopsy			0.01
Six months to one year	763 (25)	827 (33)	
Between one and two years	1484 (48)	1006 (40)	
Two to five years	819 (27)	699 (28)	
Calendar period of follow-up biopsy			<0.01
≤1989	182 (6)	394 (16)	
1990–1999	993 (32)	1238 (49)	
≥2000	1891 (62)	900 (36)	
Level of education			<0.01
Missing data	42 (1)	59 (2)	
<2 years of high school	700 (23)	804 (32)	
Two years of high school	610 (20)	523 (21)	
Three years of high school	621 (20)	517 (20)	
College/University	1093 (36)	629 (25)	
Developed any infection during follow-up	597 (19)	619 (24)	<0.01

Outcome: Diagnosis of infectious disease

Data on infectious disease were obtained from the Swedish Patient Register.[19] This register began in 1964, became nationwide in 1987, and added

hospital-based outpatient data in 2001. Our earlier validation has shown that 85%–95% of the recorded diagnoses are correct.[19] Infectious disease was defined as having a primary or secondary diagnosis of any infection (relevant International Classification of Disease (ICD) codes are presented in the appendix), or a diagnosis specifically of sepsis, streptococcal infection, influenza, *Clostridium difficile*, herpes zoster and pneumococcal infection. We chose to examine the mentioned infections since they have either been linked to CD (sepsis, *pneumococci*, influenza, *Clostridium difficile*), since they are more likely to occur in immunocompromised hosts (e.g. herpes zoster) or because they constitute a common cause of bacterial infection (e.g. *streptococci*). In our main analysis we considered only first-time infections.

Statistical considerations

We used the Cox proportional hazards model to compare the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) of incident diagnosis of infections among individuals with persistent VA vs individuals with mucosal healing on follow-up biopsy. Follow-up time started from the day of the follow-up biopsy and ended on the date of death, emigration, outcome or December 31, 2009, whichever came first. The proportional-hazards assumption was assessed using log-minus-log curves and found to be valid.

The analyses were adjusted for the following covariates: age at follow-up biopsy, sex, duration of CD at the time of follow-up biopsy (1–2 or 2–5 years vs 0.5–1 years), calendar period of follow-up biopsy (1990–1999, 2000–2009 vs –1989), and educational attainment (five categories; see Olén et al. for more information on education[20]). For children with missing data on education we used the highest educational attainment of either parent. We also performed analyses according to the following three pre-specified time strata: <1 year, 1–5 years, and >5 years after the patient's follow-up biopsy and further stratified analyses by age, sex, and calendar period of follow-up biopsy. We also conducted separate analyses for specific infections: sepsis, streptococcal infection, influenza, *Clostridium difficile*, herpes zoster and pneumococcal infection.

Finally we examined the risk of any future infection also including individuals who had a record of infection before follow-up biopsy (in total $n = 7648$).

As CD has been linked to immunoglobulin (Ig)A deficiency,[21] and IgA deficiency is an independent risk factor for infections,[22] we adjusted for IgA deficiency in an additional analysis.

Since the Swedish Patient Register is based on hospital visits and admissions, less-serious infections are underrepresented. In a sensitivity analysis we redefined our definition of infection as either a record of infection *or* a prescription of antibiotics according to the Prescribed Drug Register.[23] Antibiotics were defined according to the relevant Anatomical Therapeutic Chemical (ATC) code (J01).

In a post hoc power analysis (alpha = 0.05), we had 80% power to detect an 18% increased risk of infections in CD patients with persistent VA (sample size calculator *STPlan 4.5*, MD Anderson Cancer Center).

We used SAS version 9.4 (Cary, NC) for all statistical analyses.

Results

Characteristics of patients who underwent follow-up biopsy

In total 5598 CD patients were included in the analyses; 65% were female (Table 1) and 45% had persistent VA. Slightly less than half underwent follow-up biopsy 12–24 months after the diagnostic biopsy. More than 90% of patients had their follow-up biopsy in 1990 or later. As described earlier, all characteristics described in Table 1 were associated with mucosal healing pattern.[24] Median time of follow-up was 7.9 years for those without VA on control biopsy and 11.2 years for those with persistent VA, corresponding mean and total number of person-years were 9.1 vs 11.8 and 27,809 vs 29,836, respectively.

Risk of infectious disease diagnosis according to follow-up biopsy

Among CD patients with persistent VA, 619 (24%) had a subsequent infection compared with 579 (19%) of those with mucosal healing ($p < 0.01$). Adjusting for age-group rendered the association non-significant (HR = 0.93; 95% CI = 0.82–1.04) and after additional adjusting for sex, calendar period, time between biopsies and education, persistent VA was not associated with later infection (HR = 0.99; 95% CI = 0.88–1.11). Time between diagnostic and follow-up biopsy did not influence risk estimates (<1 year: HR = 1.01; 1–5 years: HR = 1.02; and >5 years: HR = 1.01, Table 2). Risk of infection in persistent VA was similar in females (HR = 1.01) and males (HR = 0.95). We likewise did not see any effect of persistent VA on the risk of infection when stratifying by age group (Table 3), although the HR in patients aged ≥60 years on follow-up biopsy was of borderline significance (HR = 1.30 95% CI = 1.00–1.69).

Restricting our analysis to patients with a follow-up biopsy in the year 2000 or later, persistent VA was not

Table 2. Association of persistent villous atrophy with infections overall, and stratified by time after follow-up biopsy.

Stratum	Number of events	Adjusted[a] HR (95% CI)	*p* value
Overall			
Mucosal healing	597	1.0	
Persistent VA	619	0.99 (0.88–1.11)	0.85
<1 year			
Mucosal healing	81	1.0	
Persistent VA	55	1.01 (0.70–1.45)	0.97
One it five years			
Mucosal healing	230	1.0	
Persistent VA	178	1.02 (0.83–1.25)	0.88
>5 years			
Mucosal healing	286	1.0	
Persistent VA	386	1.01 (0.86–1.18)	0.95

HR: hazard ratio; VA: villous atrophy; CI: confidence interval.
[a]Adjusted for patient age at follow-up biopsy, gender, calendar period of follow-up biopsy, education, and duration of celiac disease at the time of follow-up biopsy.

Table 3. Association of persistent villous atrophy with infectious diseases, stratified by gender, age, and year of celiac disease (CD) diagnosis.

Stratum	Number of events	Adjusted[a] HR (95% CI)
Sex		
Male		
Mucosal healing	205	1.0
Persistent VA	228	0.95 (0.78–1.16)
Female		
Mucosal healing	392	1.0
Persistent VA	391	1.01 (0.87–1.17)
Age at follow-up biopsy		
<20		
Mucosal healing	281	1.0
Persistent VA	238	0.88 (0.73–1.07)
20–39		
Mucosal healing	105	1.0
Persistent VA	68	1.09 (0.79–1.49)
40–59		
Mucosal healing	121	1.0
Persistent VA	152	1.07 (0.83–1.37)
≥60		
Mucosal healing	90	1.0
Persistent VA	161	1.30 (1.00–1.69)
Calendar year of follow-up biopsy		
1989 and before		
Mucosal healing	48	1.0
Persistent VA	125	1.28 (0.91–1.80)
1990–1999		
Mucosal healing	252	1.0
Persistent VA	331	0.94 (0.79–1.11)
2000–2009		
Mucosal healing	297	1.0
Persistent VA	163	1.10 (0.90–1.34)

HR: hazard ratio; VA: villous atrophy; CI: confidence interval.
[a]Adjusted for patient age at follow-up biopsy, gender, calendar period of follow-up biopsy, education, and duration of celiac disease at the time of follow-up biopsy.

associated with future infections (HR = 1.10; 95% CI = 0.90–1.34).

Examining the risk of infection according to time between diagnostic and follow-up biopsy showed HRs close to 1 (0.5 to <1 year since first biopsy: HR = 1.12 (95% CI = 0.90–1.41); 1–2 years: HR = 1.00 (95% CI = 0.83–1.20); and >2–5 years: HR = 0.92 (95% CI = 0.74–1.14)).

Adjusting for IgA deficiency did not alter the results (HR = 0.99; 95% CI = 0.88–1.11),

When we widened our definition of infectious disease to include prescriptions of antibiotics, our HR was slightly decreased (HR = 0.93; 0.86–0.99).

Finally, in a sensitivity analysis we included all individuals with a follow-up biopsy 0.5–5 years after diagnostic biopsy (also those with a record of infection prior to follow-up biopsy). In none of this larger group of CD patients was persistent VA linked to future diagnosis of infection (HR = 1.02; 95% CI = 0.93–1.12).

Future risk of specific infections

Persistent VA was not associated with sepsis, streptococcal infection, influenza, *Clostridium difficile*, herpes zoster and pneumococcal infection (Table 4).

Discussion

In this population-based study of more than 5000 individuals with CD undergoing follow-up biopsy, we examined the risk of infections according to mucosal healing. Despite the occurrence of hospital-diagnosed infections in about 1200 of these patients, we found no association between persistent VA and subsequent risk of infection. This contrasts with our earlier findings that persistent VA increases the risk of certain CD complications such as lymphoproliferative malignancy[12] and hip fracture.[13] We had otherwise hypothesized that persistent VA would be a risk factor for future infectious disease due to persisting hyposplenism, undernutrition with micronutrient deficiency such as vitamin D deficiency.

Table 4. Risk of specific infections in patients with celiac disease who have persistent villous atrophy on follow-up biopsy, compared to those with mucosal healing.

	Number of events	Incidence (events per individual)	Yearly incidence (events per person-year of follow-up)	Adjusted[a] HR (95% CI)
Sepsis	65	1.16%	0.11%	
Mucosal recovery	24	0.78%	0.09%	1.0
Persistent VA	41	1.62%	0.14%	1.34 (0.80–2.24)
Streptococcal infection	163	2.91%	0.28%	
Mucosal recovery	79	2.58%	0.28%	1.0
Persistent VA	84	3.32%	0.28%	1.11 (0.80–1.53)
Influenza	17	0.30%	0.03%	
Mucosal recovery	7	0.23%	0.03%	1.0
Persistent VA	10	0.39%	0.03%	1.21 (0.45–3.28)
Clostridium difficile	17	0.30%	0.03%	
Mucosal recovery	6	0.20%	0.02%	1.0
Persistent VA	11	0.43%	0.04%	1.60 (0.58–4.45)
Herpes zoster virus	23	0.41%	0.04%	
Mucosal recovery	11	0.36%	0.04%	1.0
Persistent VA	12	0.43%	0.04%	0.95 (0.41–2.20)
Pneumococcal infection	8	0.14%	0.01%	
Mucosal recovery	1	0.03%	<0.01%	1.0
Persistent VA	7	0.28%	0.02%	5.37 (0.64–44.80)

HR: hazard ratio; VA: villous atrophy; CI: confidence interval.
[a]Adjusted for patient age at follow-up biopsy, gender, calendar period of follow-up biopsy, education, and duration of celiac disease at the time of follow-up biopsy.

Hyposplenism predisposes to infections by encapsulated bacteria, and is seen in as many as one-third of all CD patients.[25] One report by Di Sabatino et al.[25] suggests that hyposplenism may be reversible and decreases with treatment of the GFD (and presumably with mucosal healing). Other research suggests that low B12 levels and low folic acid levels predispose to respiratory disease,[26] and in a recent clinical trial vitamin D3 supplementation reduced the risk of infection as well as antibiotic consumption.[27,28] Micronutrient deficiencies are particularly common in untreated CD and if the malabsorption is improved by treatment with the GFD, patients with mucosal healing may have fewer infections than patients with persistent VA. This being a registry-based study, we cannot explain why rates of infections do not seem to decrease with mucosal healing. It is, however, possible that hyposplenism remains even after mucosal healing and explains why individuals with mucosal healing have a similar number of infections as those with persistent VA.

Earlier literature

Earlier literature on mucosal healing and infections is scarce. When Rubio-Tapia et al. examined mortality in patients with follow-up biopsy, 10/11 patients who died during follow-up had persistent VA.[29] Although most deaths were due to cancer, a 67-year-old male died from streptococcal meningitis. Meningitis-associated streptococci are polysaccharide-encapsulated bacteria that more often occur in hyposplenic individuals.[30]

In contrast, there are many papers on infection in CD. Although a recent British study failed to demonstrate an overall increased risk of community-acquired pneumonia in patients with CD,[31] some data suggest an excess risk for pneumococcal pneumonia (although no overall estimate is presented for pneumococcal pneumonia[31]). In a separate analysis of CD patients under the age of 65 years without vaccination against pneumococcal pneumonia, there was an increased risk of community-acquired and pneumococcal pneumonia, but because of the lack of data on follow-up biopsy appearance, Zingone et al. were unable to assess the importance of mucosal healing in their study.[31] In the current study we found no significantly increased risk of either sepsis (HR = 1.37; 95% CI = 0.81–2.29) or pneumococcal infection (HR = 5.44; 0.65–45.42) in patients with persistent VA, although our power in the pneumococcal analysis was limited as demonstrated by the wide CI. Future studies on mucosal healing and

infectious disease may choose to focus on pneumococcal infections, and also to include primary health care diagnoses in their models, since not all infections require hospital contact. Considering that our paper focused on infections needing medical attention in a hospital, our results are primarily valid for severe infections rather than mild ones.

Strengths and limitations

To our knowledge this is the first comprehensive examination of mucosal healing and the risk of infections. This is a nationwide population-based study spanning almost 40 years. The current study included more than 5000 patients undergoing follow-up biopsy (a subanalysis was based on 7600 individuals), and we had an 80% power to detect an 18% increased risk of infection after follow-up biopsy. The large number of positive events allowed us to carry out clinically relevant stratified analyses. We have previously shown that persistent VA is more common in males and in individuals with lower education, but also differs by calendar period.[24] We adjusted for all these covariates and in a sensitivity analysis also for IgA deficiency (also linked to CD[21]). Still, residual confounding may have influenced our results. For example, smoking (which we did not measure) has been linked to a lower risk of CD in some studies,[32] albeit not in Sweden.[33,34] Its relationship to mucosal healing in CD is unknown. Neither did we have any data on vaccinations. Should individuals with persistent VA have higher rates of vaccinations, this could conceal a positive association between persistent VA and certain infections. However, it is unlikely that CD patients with poor dietary adherence (resulting in persistent VA) would be more likely to consider health-promoting actions including these vaccinations.

We used biopsy registers to identify individuals with CD. Throughout the study period, small-intestinal biopsy was the gold standard for CD diagnosis both in children and adults. In a prior validation study,[17] 95% of a random sample of patients with VA had CD according to patient charts and we expect the figure to be even higher in this dataset where everyone also underwent a follow-up biopsy. During the study period, biopsy was performed by 96% of all adult gastroenterologists and 100% of pediatricians in $\geq$90% of patients undergoing work-up for CD.[17] Although we did not have data on CD serology, 88% of validated individuals had positive CD serology at time of diagnosis.[17]

We are unaware of any validation of our infectious disease outcome measures in the Swedish Patient Register except for sepsis. When Gedeborg et al. examined community-acquired sepsis in patients in Swedish intensive care units, they found a specificity of 99.4%, and for pneumonia 98.6%.[35] Still, we admit that the specificity of infections not requiring intensive care is likely lower. Overall we therefore expect a positive predictive value for infections in line with the data for other diseases (85%–95% correct diagnoses).[19] Finally, the large number of analyses in our study increases the risk of type 1 error (i.e. to erroneously reject a true null hypothesis). We believe that the association between persistent VA and a 7% lower risk of infections when we included antibiotics prescriptions in our outcome is a chance finding.

In conclusion, in patients with CD, mucosal healing does not influence the elevated risk of having a serious infection that needs hospital-based medical attention.

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Dr Ludvigsson is guarantor of this article.

Author contributions are as follows: study concept and design: LE, BL, PHRG, JAM, KM, JFL; acquisition of data: LE, JFL; analysis and interpretation of data: LE, BL, PHRG, JAM, KM, JFL; drafting of the manuscript: LE, JFL; critical revision of the manuscript for important intellectual content: LE, BL, PHRG, JAM, KM, JFL; statistical analysis: LE; and funding: JFL. All authors approve the final manuscript submitted and they approve the authorship list.

Declaration of conflicting interests

None declared.

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Ethics approval

This project (2006/633-31/4) was approved by the Research Ethics Committee of the Karolinska Institute, Sweden, on June 14, 2006.

Informed consent

The ethics review board approved this project and did not require informed consent from study participants since this was a strictly registry-based study.

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Appendix

International Classification of Disease (ICD) codes

Any infection: *ICD7* and *ICD8*: 000–134; 320; 380–383; 460–486; 491.02; 566, 567.00–01; 569.00, 590, 595, 680–684; 710, 720; *ICD9*: 000–134; 320; 380–383; 460–466; 480–487; 491B; 566, 567A+B; 590, 595, 680–686; 711A, 730; 770–771; *ICD10*: A00–B99, G00–G02; G04.2; G06–G07; H66; H70.0–1; J00–J22; J32, J35.0; N10–11, L00–L04; L08, L30.3; M00–01; P23, P35–39; and any of the below codes.

Sepsis: *ICD7*: 053, 057.1; *ICD8*: 036.0, 036.1, 038.0–2, 038.8, 038.99; *ICD9*: 036C, 038; *ICD10*: R65.0, R65.1, A39.2, A40–41

Streptococcal infection: *ICD7*: 0.53.0; *ICD8*: 0.38.0; *ICD9*: 0.38A; *ICD10*: A40.0–2

Pneumococcal infection: *ICD7*: 0.53.2; *ICD8*: 0.38.2; *ICD9*: 0.38C; *ICD10*: A40.3

Herpes zoster: *ICD7*: 088; *ICD8*: 053; *ICD9*: 053; *ICD10*: B02

***Clostridium difficile*:** *ICD10*: A04.7 (before 1997, the Swedish ICD system did not distinguish between *Clostridium difficile* and enteral infections from campylobacter, staphylococci or yersiniosis).

Influenza: ICD7 480–483; ICD8 470–474; ICD9: 487; ICD10: J10–J11.