# Very low rates of Helicobacter pylori infection in organ transplant recipients presenting with peptic ulcer disease

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## Abstract

***Background :*** **Leading causative factors of peptic ulcer disease (PUD) in the general population are infection with Helicobacter pylori (HP) and exposure to non-steroidal anti-inflammatory drugs (NSAID). We hypothesized that this may be different in transplant recipients given increased exposure of immunosuppressive and anti-microbial drugs.**

***Methods :*** **We performed a retrospective single center analysis of all patients presenting with PUD to the endoscopy unit at a tertiary care and transplant center in Germany between 2006 and 2013. PUD was diagnosed by upper endoscopy. HP was identified by biopsy and histology. Organ transplant recipients were compared to non-transplant recipients (control group).**

***Results :*** **366 patients with PUD were identified in the study period. 12% (44/366) had previously received an organ transplant. 7% (3/44) of transplant recipients were found to be positive for HP compared to 25% (81/322) in the control group (p=0.007). Even when excluding patients taking proton-pump-inhibitors (PPI) from the analysis rates were similar with 30% (65/214) of the ulcers being HP positive in the control group compared to 14% (1/7) in transplant recipients (p=0.006). Furthermore, in the transplant recipient group rates of being in intensive care, concurrent PPI and concurrent antibiotic medication were significantly higher than in the control group.**

***Conclusions :*** **Organ transplant recipients with PUD have lower rates of Helicobacter pylori positivity compared to the general population.** (Acta gastroenterol. belg., **2017**, 80, **25-30**).

**Key words** : endoscopy, helicobacter pylori, immunosuppression, peptic ulcer, proton-pump-inhibitors, transplantation.

## Introduction

Peptic ulcer disease (PUD) is a common affection of the upper gastrointestinal (GI) tract in both transplanted and non-transplanted patients. Although the ulcers are usually detected and treated early enough to prevent complications such as severe bleeding and perforation both do occur occasionally and can be life-threatening. In organ transplant recipients severe complications seem to occur more frequently.

Worldwide most cases of gastroduodenal ulcers are associated with an infection with the gram-negative, helix-shaped, microaerophilic bacteria *Helicobacter pylori* (HP). More than half of the world's adult population is colonized with HP. In inverse correlation with socioeconomic status the prevalence of HP-infections in developing countries is significantly higher than in developed ones (90% vs. 20% in adulthood). Worldwide up to 70% of all gastric and 95% of the duodenal ulcers are thought to be due to HP infection. In recent years, prevalence of HP infection has been decreasing while use of NSAIDs especially low-dose aspirin has been on the rise in the western world cases leading to a relative increase in non-HP associated PUD, yet HP still remains being the most important risk factor causing at least 46-60% of all PUD cases. Furthermore, HP-infection is associated with a higher risk of developing gastric adenocarcinoma or mucosa- associated lymphatic tissue (MALT) lymphoma. Another important risk factor for developing PUD is regular intake of acetylsalicylic acid or non-steroidal-anti-inflammatory drugs (NSAID) such as ibuprofen. Additional exposure to glucocorticoids further increases risk to up to 15-fold. Other risk factors for PUD include age more than sixty years, smoking, viral infection with cytomegalovirus (CMV) or herpes simplex virus (HSV), inflammatory bowel disease (IBD) especially Crohn's disease, chemotherapy, radiation therapy, other drugs (mycophenolate-mofetil, clopidogrel), chronic renal failure, hepatic cirrhosis, $\alpha$1-antitrypsin-deficiency, hyperparathyreoidism, vasculitis, gastrinoma, and polycythaemia vera.

There are only limited data available about the etiology of ulcers in post-transplant patients and previous studies have shown inconsistent results. Some suggest that the prevalence of HP decreases in patients after undergoing organ transplantation possibly as a consequence of the increased use of antibiotics and PPI in this group while other studies have shown an increased rate of HP infection or no difference at all. Our aim was to evaluate the role of HP in the etiology of PUD in patients after organ transplantation compared to non-organ transplant recipients.

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## Materials and methods

*Patient cohort and acquisition of clinical data*

We performed a retrospective chart-based analysis to identify all patients presenting with PUD to the endoscopy unit at Hannover Medical School, a tertiary care and transplant center in Northern Germany, between 2006 and 2013. PUD was diagnosed by upper endoscopy. All patients with a florid gastric or duodenal ulcer at index endoscopy and any one or more of the following HP tests were included: (1) histology report stating presence or absence of HP organisms; (2) rapid urease test (Pronto Dry urease test, Medical Instruments Corporation GmbH); (3) HP antigen stool test (Ridascreen Femtolab H.pylori, r-biopharm). Patients with malignant ulcers identified by histopathological examination were excluded from the analysis. When presence of HP infection was identified one or more of the above diagnostic assays ulcers were considered HP-positive in this analysis. Additional clinical data were obtained from patient records.

*Ethics*

The study protocol was approved by the institutional ethics committee.

*Statistics*

Data were expressed as numbers/percentages or median with range. Non-continuous parameters were analysed by Chi-square test or Fisher's exact test. P-values $< 0.05$ were considered statistically significant. A multivariate analysis (logistic regression) was performed to identify clinical risk factors for HP positive ulcers. The software used was the SPSS Statistical Package (version 19.0, SPSS Inc., Chicago, IL, USA).

## Results

Overall 30,760 upper endoscopies were performed between 2006 and 2013 at Hannover Medical School endoscopy unit and 366 individuals were identified as having PUD. Of these 44 (12%) had undergone solid organ or bone marrow transplantation (BMT) prior to being diagnosed with PUD (transplant recipients) (Table 1). The remaining 322 had not undergone organ transplantation at the time of PUD diagnosis and are here referred to as the control group.

The clinical presentation varied from no symptoms to emergency cases of upper GI bleeding. 161 individuals (41%) had clinical evidence upper GI bleeding in terms of either melena or hematemesis. Other clinical presentations included epigastric pain in 77 (21%), anaemia in 55 (15%) and dyspepsia in 37 (10%) individuals. 40 (11%) of the PUD patients had no ulcer related GI symptoms and underwent upper endoscopy for unrelated reasons. PUD patients were predominately male: 27 of 44 (61%) transplant recipients and 194 of 322 (60%) in the control group. All but one of the transplant recipients (98%) were inpatients at the time of diagnosis, twelve (28%) had been inpatients for more than one month before being diagnosed as having PUD. Of the controls 268 (83%) were in inpatient care but only a minority 18 (7%) had had inpatient status for over one month at the time of the diagnostic upper endoscopy. Within the transplant recipient group twelve out of 44 (27%) had received a liver transplant; another twelve (27%) had received a kidney transplant. The remainder had received a lung, bone marrow, heart transplant or combined organ transplant. More baseline information on the transplant and control group is summarized in Table 1.

In the transplant recipient group three of 44 (7%) were found to be HP-positive and the same three of 44

Table 1. — **Baseline patient characteristics**

| | **Transplant recipients** (n= 44) | **Controls** (n= 322) |
|---|---|---|
| **Sex (%)** | | |
| *male* | 27 (61) | 194 (60) |
| *female* | 17 (39) | 128 (40) |
| **Age (years)** | median 56,5; range 17-73 | median 64; range 18-95 |
| **Inpatient (%)** | 43/44 (98) | 268/322 (83) |
| < 7 d | 21/43 (49) | 206/268 (77) |
| *>7 d <30 d* | 10/43 (23) | 44/268 (16) |
| *> 30 days* | 12/43 (28) | 18/268 (7) |
| **Outpatient (%)** | 1/44 (2) | 54/322 (17) |
| **Tx-organ (%)** | | |
| *liver* | 12/44 (27) | n/a |
| *kidney* | 12/44 (27) | n/a |
| *allogenic SCTx* | 5/44 (11) | n/a |
| *lung* | 11/44 (25) | n/a |
| *heart* | 1/44 (2) | n/a |
| *pancreas+kidney* | 2/44 (5) | n/a |
| *liver+kidney* | 1/44 (2) | n/a |
| **Time since Tx (%)** | | |
| *<1 y* | 19/44 (43) | n/a |
| *>1y <5y* | 10/44 (23) | n/a |
| *>5y* | 15/44 (34) | n/a |

Tx-organ, transplanted organ; SCTx, stem cell transplant, Tx, transplantation

Table 2. — **Ulcer-relevant characteristics in transplant recipients vs controls**

| | **Transplant recipients (n=44)** | **Controls (n=322)** | **p-value** |
|---|---|---|---|
| **Ulcer localization (%)** | | | |
| stomach | 23/44 (52) | 166/322 (52) | 0.9286 |
| duodenum | 15/44 (34) | 107/322 (33) | 0.9095 |
| both | 5/44 (11) | 35/322 (11) | 0.9215 |
| anastomosis | 1/44 (2) | 14/322 (4) | 0.5149 |
| **Gastritis type (%)** | | | |
| A | 0/44 (0) | 1/322 (0.3) | 0.7113 |
| B | 3/44 (7) | 85/322 (26) | **0.0044** |
| C | 14/44 (32) | 106/322 (33) | 0.8840 |
| GvHD-gastritis | 1/44 (2) | 0/322 (0) | 0.0068 |
| Ischemic gastritis | 0/44 (0) | 1/322 (0.3) | 0.7113 |
| unclassified gastitis | 12/44 (27) | 99/322 (31) | 0.6383 |
| no gastritis | 4/44 (9) | 18/322 (6) | 0.3595 |
| no histopathology | 10/44 (23) | 17/322 (5) | **<0.0001** |
| **PPI therapy (%)** | 37/44 (84) | 108/322 (34) | **<0.0001** |
| **Risk factors (%)** | | | |
| Helicobacter pylori | 3/44 (7) | 81/322 (25) | **0.0067** |
| NSAID | 9/44 (20) | 111/322 (35) | 0.0632 |
| ischemic | 1/44 (2) | 3/322 (0.6) | 0.2544 |
| ICU treantment | 14/44 (31) | 8/322 (2) | **<0.0001** |
| Age >60 | 17/44 (39) | 195/322 (61) | **0.0057** |
| Steroids | 35/44 (80) | 26/322 (8) | **<0.0001** |
| Mycophenolate | 29/44 (66) | 1/322 (0.3) | **<0.0001** |
| CMV | 2/44 (5) | 0/322 (0) | **0.0001** |
| HSV | 0/44 (0) | 1/322 (0.3) | 0.7113 |
| Clopidogrel | 3/44 (7) | 20/322 (6) | 0.8763 |
| IBD | 0/44 (0) | 9/322 (3) | 0.2615 |
| Chemotherapy | 3/44 (7) | 15/322 (5) | 0.5343 |
| Radiation therapy | 0/44 (0) | 1/322 (0.3) | 0.7113 |
| Other* | 16/44 (36) | 73/322 (23) | **0.0470** |

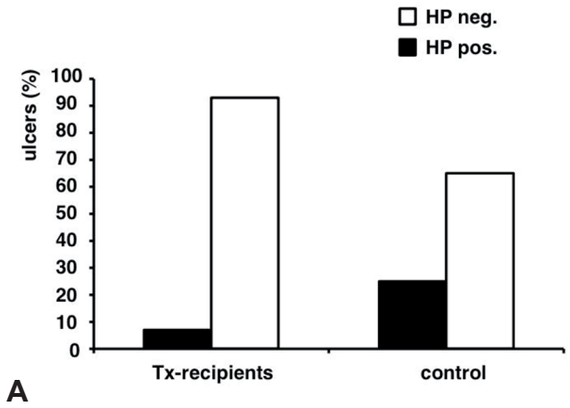
P-values were determined significant < 0.05. HP, helicobacter pylori; IS, immunosuppression; Tx, transplant recipient; PPI, proton pump inhibitor; NSAID, non-steroidal anti-inflammatory drug; ICU, intensive care unit; IBD, inflammatory bowel disease; CMV, cytomegalovirus; HSV, herpes simplex virus. * - other factors include chronic renal failure, cirrhosis, α1-AT deficiency, hyperparathyroidism, vasculitis, polycythaemia vera

(7%) also showed the histological picture of type B gastritis. The respective numbers in the control group were significantly higher with 81 of 322 PUD patients (25%; p=0.007) being HP positive and 85 (26%; p=0.004) showing type B gastritis (Table 2, Fig. 1A). A similarly significant difference (p=0.006) was observed when patients already on PPI were excluded from the analysis (Fig. 1B). Conversely, looking at all PUD patients post organ transplantation status was associated with being HP negative (Fig. 3). Other differentiating features of the transplant recipient compared to the control group included higher rate of patients in intensive care at time of PUD diagnosis, younger age, higher rate of positivity for cytomegalovirus, and more commonly being on proton pump inhibitor (PPI) therapy (Table 2). Moreover, more than half of the transplant recipients (25 of 44; 57%) took antibiotics at the time of PUD diagnosis compared to only 23 of 322 (7%) of the control-patients. There was no significant difference in exposure to NSAID at the time of PUD diagnosis. Of note, when multivariate analysis was performed on the entire PUD population to identify factors independently associated with being HP-positive only PPI use remained while there was only a sub-significant trend for post organ transplantation status.

The period of time since transplantation in post transplantation PUD patients varied from one month up to 26 years but the majority (43%) of ulcers were detected in the first year after transplantation (Fig. 2A). Forrest class and localization showed an approximately identically distribution in both groups. Slightly more than half of the detected ulcers appeared in the stomach, followed by duodenal ulcers. Eleven percent of the patients in both groups were found to have both gastric and duodenal ulcers (Fig. 2B).

29 patients (8%) of the study population (n=366) were under immunosuppressive treatment for reasons other than transplantation - most frequently rheumatoid arthritis (35%), spondyloarthropathies (17%), Crohn's disease (7%), granulomatosis with polyangiitis (7%) or autoimmune hepatitis (7%). Six out of these 29 patients (21%) were found to be HP positive compared to 75 out of 293 patients (26%) without immunosuppressive medication (p=0.4044) suggesting that the difference observed between transplanted patients and controls were not due to the effects of immunosuppression.

In the transplant recipient group five patients (11%) died within the same hospital stay the PUD was diagnosed. One of them died of gastric perforation the other four of multiple organ dysfunction syndrome (MODS)



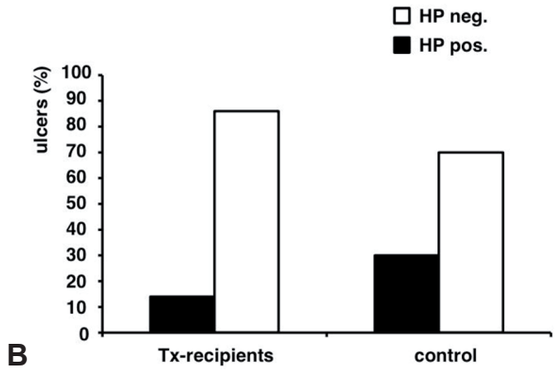
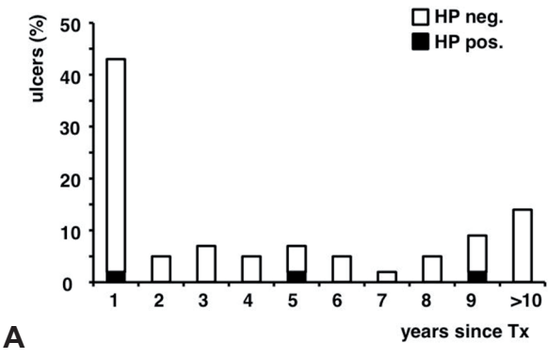




Fig. 1. — HP positive versus HP negative ulcers in transplant recipients (Tx recipients) and in controls. Percentages of HP positive and negative ulcers in (A) all transplant recipients and controls included in this study and (B) in the subgroup without PPI therapy.



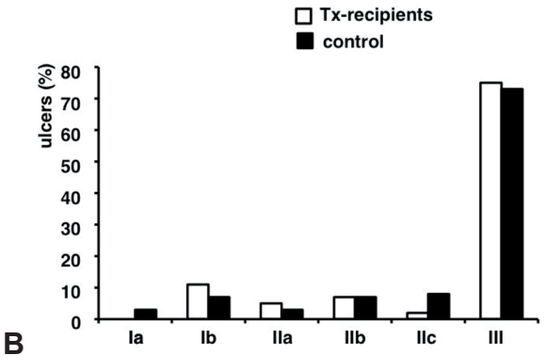




Fig. 2. — Characteristics of gastroduodenal ulcers presenting in transplant recipients. (A) Duration from transplantation until PUD diagnosis. (B) Forrest class in transplant recipients compared to controls.

aggravated by GI bleeding. None of them underwent surgery because of the ulcer. Only eight out of 322 (2%) of the control group died within the same hospital stay the PUD was diagnosed. Two of them died in haemorrhagic shock due to intractable Forrest I bleeding; the other six from MODS or respiratory failure. Four patients in the control group underwent surgery (One ulcer excision, one gastrectomy, one whipple duodenectomy and one ulcer repair).

## Discussion

While HP plays a leading role in the pathogenesis of PUD in the general population, only 23% of our tertiary care PUD population were HP positive during the study period. Especially in patients who previously had undergone organ transplantation ulcers were found to be HP positive in only 7%. Two factors may explain this finding: first, this is a heavily pre-treated patient population that has likely been exposed to one or more course of antibiotic treatment including broad-spectrum agents. So, HP may have been accidentally eradicated in many cases. Second, non-HP risk factors like treatment in an intensive care unit, severe comorbidities or exposure to glucocorticoids are more prevalent in this population and hence may contribute more to the burden of PUD compared to the general population. In keeping with this, the exposure to both antibiotics and PPI was found to be significantly higher in the transplant recipient group.

Our transplant group contained five BMT-recipients. Clearly, there are important differences between BMT and solid organ transplantat recipients. Yet, both patient populations share the need for immunosuppression in the post-transplant period and the exposure to intensive inpatient care and high likelihood of receiveing broad-spectrum and/or multiple class antibiotic treatment as well as PPI. Thus, we considered it justified to analyse them together in this study. Indeed, very low rates of HP positive ulcers were found in both groups albeit the number of BMT-recipients in our study population is low (Fig. 3).

The multivariate analysis identified PPI use to be the only remaining significant risk factor for HP negative ulcers. There was a trend towards transplant status being

associated with HP negative ulcers, but this did not reach statistical significance in the multivariate analysis. This result has to be seen in the context of the still comparatively small group of transplant recipients with PUD included in this study. PPI are known to induce false-negative results in the rapid urease-test for HP by both decreasing the activity of HP and shifting their distribution pattern to the stomach body instead of the antrum. In elective upper endoscopy patients should be instructed to stop PPI treatment two weeks before the appointment to avoid false-negative HP results. Since upper GI bleeding – evidence of which was present in 41% of patients included here – is an emergency this was impracticable in many cases. As expected, when comparing PPI users to patients without PPI treatment the HP rates were overall significantly higher in the PPI naïve group but remained low compared to the rates known from literature for the general non-transplant population. This indicates that the high rate of PPI use in our study population does not account for the low rate of HP positive ulcer. It is likely that rather the patient selection in our tertiary-care center is the explanation for our observation.

Some previously performed studies showed similar results. Akatsu et al. compared the rates of HP infection identified by gastric biopsy in 29 cases of patients both before and after undergoing liver transplantation. HP infection rates decreased from 50% in the preoperative patients to 5.6% postoperatively. Telkes et al. performed upper endoscopies in 543 kidney transplant recipients and found a high frequency of ulcers in this patient group but no correlation between HP and PUD and low HP rates (21%) in gastric biopsies. Ueda et al. compared some previously performed trials about HP incidence in kidney transplant recipients. HP positivity rates detected by rapid urease test, histology, serology or breath tests ranged from 29% to 70%. Other studies showed higher rates of HP in transplant recipients and linked this result to the immunosuppressive medication taken by these patients: Hruby et al. described a higher HP prevalence in kidney transplant recipients (62%) compared to dialysis patients (34.6%) and control patients (43.6%) all presenting with dyspepsia but an overall low prevalence of active inflammatory lesions in transplant recipients. Most studies were performed on kidney transplant recipients showed no difference in HP rates compared to the normal population. A reason for this could be that many patients included were outpatients long-term after transplantation. Telkes et al. described in their study population of kidney transplant recipients that the most vulnerable period for developing PUD is the first three months after undergoing transplantation. In line with this, in our study population nearly half of all ulcers in transplant recipients occurred in the first year after surgery.

Even in the setting of a bleeding ulcer HP eradication is not recommended unless its presence has been detected by appropriate testing. However, in clinical practice especially in the setting of severe bleeding endoscopists may opt against taking biopsies and thus clarification of HP status may be delayed. Our data, underscore that especially in a population of transplant recipients there is no case for empiric eradication since the rates of HP positive ulcers are surprisingly low.

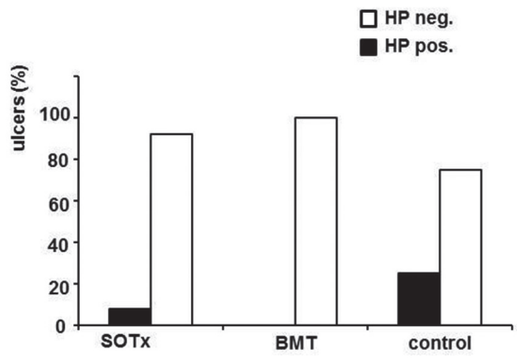



Fig. 3. — Percentages of HP positive versus HP negative ulcers in solid organ transplant recipients (SOTx), in bone marrow transplant recipients (BMT) and in controls

In summary, our data indicate that the etiology of PUD in patients after organ transplantation is different from what is known for the general population. Most notably, HP positivity is rare and other etiological factors predominate. This data may inform clinical decision making in the care of transplant recipients. Whether the findings can be generalized to other heavily pretreated inpatient populations will need to be clarified in future studies.

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