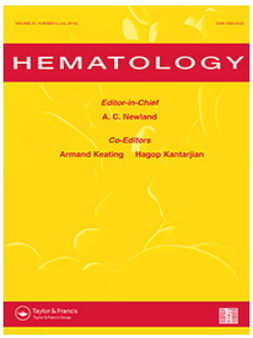

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Association of proton pump inhibitors with the occurrence of gut-derived bacteraemia in patients with haematological malignancy after chemotherapy

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Background: Gut-derived bacteraemia is a major complication in patients with haematological malignancy after chemotherapy.
Objective: Our study aimed to investigate the role of proton pump inhibitors (PPIs) in the occurrence of gut-derived bacteraemia.
Methods: We compared data from 92 hospitalized haematological malignancy patients after chemotherapy with gut-derived bacteraemia, collected from January 2009 to July 2015, with those of 92 contemporaneous, hospitalized haematological malignancy patients without bacteraemia. We evaluated PPIs use and analysed the effects of covariates.
Results: Patients with gut-derived bacteraemia had a significantly higher incidence of PPIs use (69.6%) than that of controls (47.8%). Of the patients with gut-derived bacteraemia, only 44.6% had a documented indication for PPIs therapy. The antibacterial prophylaxis rate was 38.0% in the bacteraemia group and 58.7% in the non-antibacterial group. Based on multivariable logistic regression analysis, only PPIs use ($P = 0.00$, odds ratio (OR) = 0.546) was found to be associated with the risk of bacteraemia whereas antibacterial prophylaxis ($P = 0.00$, OR = 0.652) was protective. There were no significant differences in demographics, malignancy status, length of neutropenia, complications, or steroid use between the gut-derived bacteraemia and control group.
Conclusions: This study suggests a potential association between PPIs use and development of gut-derived bacteraemia in haematological malignancy patients after chemotherapy.

Keywords: Hematologic malignancy, Gut-derived bacteraemia, Proton pump inhibitor (PPI), Prophylactic antibiotics

Introduction

Bacteraemia is a major complication after chemotherapy in patients with haematological malignancy.[1] The prevalence ranges from 12 to 16.4% after chemotherapy in haematological malignancy patients,[2,3] and 56–65% of such cases in developing countries suffer from gut-derived bacteraemia, which carries a very poor prognosis; indeed, the short-term mortality rate is ~25% even when the diagnosis is made early and treatment started rapidly.[4–7] Gut-derived bacteraemia usually originates from the intestine.

Gut-derived bacteraemia is resulted from bacterial translocation across the intestinal wall to mesenteric lymph nodes and then into the bloodstream. Bacteraemia may occur due to alterations of the host immune system, disruption of the normal indigenous bacterial flora, loss of the mucosal barrier, and among other causes.

Proton pump inhibitors (PPIs) are frequently administered to haematological patients during and after chemotherapy for diverse reasons. PPIs are commonly prescribed for dyspepsia and acid peptic disease, for routine stress ulcer prophylaxis, for prevention of non-steroidal anti-inflammatory drug-induced ulcers, etc. PPIs were also found to have the function to lower tolerance to chemotherapy,[8] and to reduce tumour burden and metastasis.[9] So that, PPIs are commonly used in haematological department. PPIs use may have potential harmful effects and, in particular,

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carries a risk of bacterial infection.[10–12] PPIs are designed to shut down the gastric proton pump (H^+/K^+-ATPase) of parietal cells, thereby increasing the pH of the stomach and facilitating proliferation of intestinal bacteria.[11,13,14] PPIs may also impair gastrointestinal motility,[15] predisposing to bacterial translocation.[16] In addition, impairment of neutrophil function by PPIs, which increases the risk of bacterial infection, has been reported.[17–19] Currently, whether PPIs increase the risk of gut-derived bacteraemia remains unclear.

In this study, we compared the prevalence of PPIs use in patients with haematological malignancy with versus without gut-derived bacteraemia. We sought to investigate the role of PPIs in the occurrence of gut-derived bacteraemia and to determine whether PPIs treatment is appropriate in haematological malignancy patients during and after chemotherapy.

Patients and methods

Patients

In our retrospective case-control study, we identified the medical records of all patients with a confirmed diagnosis of bacteraemia admitted to the Haematology Department of a large urban tertiary care facility between January 2009 and July 2015. This research has been approved by our Institutional Review Board, and patient records was anonymized and de-identified prior to analysis. We included patients who suffered from bacteraemia and excluded those who suffered from lung and upper respiratory airway infection, urinary tract infection, perianal infection, catheter-related infection, skin infection, oral mucositis, and surgery patients, and the patients who recovered from bacteraemia recently. We also excluded patients who underwent bronchoscopy, gastroscopy, parenteral nutrition, and bladder catheter before bacteraemia within the preceding 7 days and those patients with gastrointestinal bleeding within the preceding 14 days.

Microbiological evaluations, which included two separate blood samples obtained from two different anatomical sites for culture, were performed at the onset of fever, according to standard practice. In the absence of an indwelling central venous catheter, two blood samples were obtained from two distinct peripheral veins. When an indwelling central venous catheter was present, one blood sample was obtained through this catheter, and a second was obtained from a peripheral vein.

The diagnosis and source of bloodstream infection were determined by the physician in charge and a specifically trained nurse and were based on objective clinical evidence, microbiological data, and clinical judgment. Blood cultures were performed in aerobic and anaerobic bottles and incubated in an automatic system. Bacteraemia was identified using standard microbiological methods. Gut-derived bacteraemia cases (group 1) were defined as patients who met the inclusion and exclusion criteria. The non-bacteraemia patients (group 2) were haematology disease patients who underwent chemotherapy but were negative for bacteraemia (negative blood culture). All patients were admitted during the study period. Age, gender, underling malignancy, malignancy status were compared between the two groups as well.

PPIs use and its therapeutic indications were assessed in the two groups by reviewing medical charts. Patients who received PPIs for at least 1 week prior to bacteraemia in group 1 and for at least 1 week during and after chemotherapy in group 2 were considered as being treated with PPIs, regardless of the dose. Other patients were considered non-users. A single dose of PPIs did not constitute PPIs use. Therapeutic use was defined as appropriate if it corresponded to an indication strongly supported by the medical literature.[20–22] Acceptable indications for PPIs use were limited to gastro-oesophageal reflux disease, peptic ulcer disease and *Helicobacter pylori* eradication, Barrett's oesophagus, Zollinger–Ellison syndrome, and prevention of non-steroidal anti-inflammatory drug-induced ulcers and pathologic hypersecretory conditions. Data were collected using an anonymous standardized case-record form. Patient data consisted of demographic characteristics (age, gender), underlying malignancy, malignancy status, white blood cell count at the time of bacteraemia diagnosis, duration of neutropenia, antibacterial prophylaxis (we prescribed fluoroquinolone for the patients as antibacterial prophylaxis following the 2008 NCCN guideline for prevention and treatment of cancer-related infections) and corticosteroid therapy, and complications.

Statistical analysis

Data are expressed as percentages or medians (95% confidence intervals (CIs)). Statistical analysis was conducted using the chi-squared test, independent-samples *t*-test, and logistic regression. All statistical testing was two-tailed at the 5% level. The role of PPIs use and other factors potentially associated with bacteraemia was assessed by comparing patients in groups 1 and 2. A multivariable logistic regression analysis was performed to assess the association of PPIs use with the occurrence of bacteraemia while adjusting for other factors. All statistical analyses were performed using the SPSS 13.0 software.

Results

The medical charts of 493 haematological malignancy patients after chemotherapy with bacteraemia were reviewed. Confirmed gut-derived bacteraemia was

found in 92 cases. The non-bacteraemia patients were matched for age, gender, underlying malignancy, and the status of the underlying malignancy and were admitted to our hospital within 6 months of the study admission date.

The clinical characteristics of patients in the two groups are shown in Table 1. There was no significant difference in baseline parameters between the two groups.

There were no differences in the median duration of neutropenia between the groups. During their hospitalization, 84.3% of patients ($n = 184$) had neutropenia for a median duration of 7.7 days. The in-hospital mortality rate in group 1 was 6.5% ($n = 92$).

The pathogens isolated from blood cultures are shown in Table 2. Gram-negative bacilli were the predominant isolates, accounting for 82.6% of the total. The most common enteric organisms were *Escherichia coli* (38.0%), *Klebsiella pneumoniae* (26.1%), and *Enterobacter cloacae* (7.6%). Nine patients (9.8%) suffered from bacteraemia caused by Gram-positive organisms, of which *Streptococcus viridans* was the predominant isolate (5.4%). Seven (7.6%) of the 92 patients had polymicrobial infections (two to three pathogens). All six hospital deaths in the group were attributed to bacteraemia, of which four were Gram-negative, two were polymicrobial bacteraemia.

The proportion of haematological malignancy patients with gut-derived bacteraemia taking PPIs was 69.6%, compared with only 47.8% of those without bacteraemia; this difference was significant ($P = 0.004$). Of the patients with gut-derived bacteraemia, only 44.6% had a documented indication for PPIs therapy. No significant differences were observed between bacteraemia and non-bacteraemia patients with regard to indications for PPIs prescription, the routes of administration of PPIs (i.v. vs. p.o.), or dosage of PPI (q.d. vs. b.i.d.) (Table 3).

Antibacterial prophylaxis was administered to 89 (48.9%) patients. The antibacterial prophylaxis rate was 38.0% in group 1 and 58.7% in group 2 (Table 4) ($P = 0.008$). The use of prophylactic antibiotics had a trend towards influencing the type of pathogen causing bacteraemia (Table 5), albeit not significantly so. Bacteraemia caused by Gram-negative organisms was associated with a 4.3% mortality rate, while no deaths due to bacteraemia caused by Gram-positive organisms were observed (Table 2).

A logistic regression analysis was performed with bacteraemia as the outcome (Table 6), in which only parameters significantly different in the multivariable analysis, i.e. PPIs use and antibacterial prophylaxis, were included. There were no statistically significant differences in demographics, status of malignancy, length of neutropenia, complications, and steroid use between the groups. PPIs use ($P = 0.00$, odds ratio (OR) = 0.546) were associated with bacteraemia, and

Table 1 Characteristics of patients with and without gut-derived bacteraemia

Characteristic	Group 1 (bacteraemia) ($n = 92$)	Group 2 (non-bacteraemia) ($n = 92$)	*P*
Demographics			
Age, years*	43.2 ± 15.6	43.5 ± 15.0	0.878
Male, *n* (%)	45 (48.9)	48 (52.1)	0.768
Underlying malignancy			
ALL, *n* (%)	20 (21.7)	18 (19.6)	0.856
AML, *n* (%)	55 (59.8)	57 (62.0)	0.880
NHL, *n* (%)	11 (12.0)	11 (12.0)	1.00
MDS, *n* (%)	4 (4.3)	4 (4.3)	1.00
MM, *n* (%)	2 (2.2)	2 (2.2)	1.00
Status of malignancy CR, *n* (%)	42 (45.7)	42 (45.7)	1.00
Length of neutropenia, days*	7.8 ± 3.9	7.6 ± 6.6	0.807
Diabetes mellitus, *n* (%)	4 (4.3)	4 (4.3)	1.00
Hepatitis B, *n* (%)	10 (10.9)	7 (7.61)	0.612

*Data are expressed as medians (95% CIs).
ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; NHL, non-Hodgkin's lymphoma; MDS, myelodysplastic syndrome; MM, multiple myeloma; CR, complete remission.

Table 2 Pathogens and mortality rates

Causative pathogen	Rate ($n = 92$) (%)	Mortality rate ($n = 92$) (%)
Gram-negative	76 (82.6)	
E. coli	35 (38.0)	3 (3.3)
K. pneumoniae	24 (26.1)	1 (1.1)
E. cloacae	7 (7.6)	
Pseudomonas aeruginosa	5 (5.4)	
Proteus mirabilis	2 (2.2)	
Enterobacter agglomerans	1 (1.1)	
Enterobacter aerogenes	1 (1.1)	
Chryseobacterium indologenes	1 (1.1)	
Gram-positive	9 (9.8)	
S. viridans	5 (5.4)	
Leuconostoc pseudomesenteroides	4 (4.3)	
Polymicrobial bacteraemia	7 (7.6)	2 (2.2)

Table 3 Details of PPI use

	Group 1 (bacteraemia) ($n = 64$)	Group 2 (non-bacteraemia) ($n = 44$)	*P*
i.v. administration (%)	23 (35.9)	19 (43.2)	0.430
q.d. PPI dosage (%)	51 (79.7)	33 (75)	0.817
Appropriate PPI therapy (%)	29 (45.3)	22 (50)	0.696

q.d., every day.

Table 4 Acid-suppressive therapy and other medications

Factor	Group 1 (bacteraemia) (*n* = 92) (%)	Group 2 (non-bacteraemia) (*n* = 92) (%)	*P*
PPIs use, *n* (%)	64 (69.6)	44 (47.8)	0.004
Antibacterial prophylaxis, *n* (%)	35 (38.0)	54 (58.7)	0.008
Steroid use, *n* (%)	24 (26.1)	22 (23.9)	0.865

Table 5 Prophylaxis and the causative pathogen of bacteraemia

Causative pathogen	Prophylaxis (*n* = 35)	Non-prophylaxis (*n* = 57)	*P*
Gram-negative, *n* (%)	25 (71.4)	51 (89.5)	0.177
Gram-positive, *n* (%)	5 (14.3)	4 (7.0)	
Complex bacteraemia, *n* (%)	5 (14.3)	2 (3.5)	

antibacterial prophylaxis ($P = 0.00$, OR = 0.652) were negative correlation with bacteraemia.

Discussion

In recent years, PPIs have been associated with several adverse events, including pneumonia,[23] *Clostridium difficile* infection,[24] hip fracture,[25] interstitial nephritis,[26] low serum magnesium and vitamin B12 levels,[27] decreased iron absorption,[27] and increased cardiac birth defects during pregnancy.[28] Newer evidence now associates PPIs with spontaneous bacterial peritonitis[29,30] and *C. difficile* infection in patients with cirrhosis.[10] Our data support an association between PPIs and the development of gut-derived bacteraemia.

Use of PPIs is increasing in China despite the fact that the approved indications for PPIs use are selective and usually for a limited duration. Studies have shown the occurrence of inappropriate use of acid-suppressive therapy in hospitalized patients.[31,32] Because of their perceived safety, PPIs have come to be prescribed for a variety of non-approved indications, often for indefinite periods of time.[33] Up to 71% of patients in general medicine wards receive some sort of acid-suppressive therapy without an appropriate indication.[34] There is limited evidence to support the use of chronic acid suppression in patients during and after chemotherapy. There is no evidence suggesting that PPIs have a role in preventing or treating chemotherapy-induced nausea and vomiting. In our study, reasons for PPI therapy were either inappropriate or else undocumented in half of the cases. This suggests the need for strict adherence to the guidelines concerning PPI use in haematological malignancy patients during and after chemotherapy.

Table 6 PPIs use and gut-derived bacteraemia: multivariable logistic regression analysis

Factor	Multivariable *P*-value
Age	0.394
Male	0.269
Status of malignancy (CR)	0.149
Length of neutropenia	0.806
Diabetes mellitus	0.397
Hepatitis B	0.234
PPIs use	0.000
Antibacterial prophylaxis	0.000
Steroid use	0.334

The mechanism by which gastric acid suppression might lead to an increased incidence of bacteraemia is poorly understood. The gastrointestinal tract is a primary reservoir for opportunistic bacteria. Study had found bacterial overgrowth in hypochlorhydric subjects,[35] the suppression of gastric acid secretion results in gastric bacterial overgrowth[36] and duodenal bacterial overgrowth.[37,38] Gastric acid suppression can also reduce the primary barrier to bacteria within the gastrointestinal tract, and when combined with the intestinal permeability impairment seen in haematological malignancy after chemotherapy, it sets the stage for higher bacterial counts within the small intestine.[15,18,19] The risk of enteric infections has been reported to be 2.5-fold greater in patients on acid-suppressive therapy compared with patients not receiving acid-suppressive therapy.[39] Bacteria within the gut can cross the gastrointestinal mucosal barrier and spread systemically by a process termed bacterial translocation. Factors that can trigger bacterial translocation from the gut include host immune deficiencies and immunosuppression, disturbances in the normal gut ecological balance, and mucosal barrier permeability. So the patients who received PPIs in our study were easily suffered from bacteraemia.

Therapies directed at preventing or limiting bacterial translocation are based on maintaining the host's physiologic defences, which include maintaining a stable gut flora, normal intestinal barrier function, and limiting chemotherapy-induced gut injury. Therefore, the inappropriate use of acid-suppressive therapy should be reduced or stopped. The major clinical therapeutic approach directed at limiting intestinal bacterial overgrowth with potential pathogenic bacteria is selective digestive tract decontamination.[40] In haematological malignancy patients after chemotherapy who undergo bone marrow suppression, the use of oral non-absorbable antibiotics plus a brief course of systemic antibiotics prevents intestinal bacterial overgrowth and thereby limits gut-derived bacteraemia.

As found in this study, prophylactic antibiotics reduce the rate of gut-derived bacteraemia. The antibacterial prophylaxis rate was 38.0% in the gut-derived bacteraemia group, compared with 58.7% in the non-gut-derived bacteraemia group; this difference was significant. The use of prophylactic antibiotics tended to affect the type of pathogen causing bacteraemia, with only 71.4% caused by Gram-negative organisms compared with 14.3% by Gram-positive organisms. If no prophylactic antibiotics were given, the rates were 89.5 and 7.0%, respectively, though it was of no significantly difference, but if we include more patients in the bacteraemia group, it might have resulted in detection of a significant difference. Feld[41] found that among patients who received prophylactic antibiotics, Gram-positive bacteraemia was far more common than Gram-negative bacteraemia (75 vs. 25%), compared with ~50% each in patients who did not undergo prophylactic antibiotic treatment.

Our study had several limitations. Firstly, our results suggested an association between bacteraemia and PPIs use. However, an association does not prove causation. We could not confirm that the organisms isolated actually originated from the gut. Only a single objective inclusion criterion was used; i.e. a positive blood culture, although several exclusion criteria were applied. However, we did not culture gastric juice simultaneously with blood. Therefore, it was possible that the organisms originated from a site other than the gut. Moreover, determining the origin of organisms in the neutropenia patients was more difficult. Other limitations of the study included its retrospective design, the limited number of patients, and the fact that patients were not matched for certain factors, such as the intensity of chemotherapy. Although the strong association of PPIs use with bacteraemia suggests a causal relationship, other explanations are possible. PPIs may have been prescribed for dyspeptic symptoms associated with impaired small bowel motility, and such patients may have pre-existing bacterial overgrowth, which can predispose to bacteraemia. Symptoms of abdominal pain resulting from abdominal wall tension may have been treated with PPIs in some cases, and patients with these symptoms may have a greater predisposition to bacteraemia.

Future investigations into the association between acid suppression and bacteraemia appear warranted. A prospective, randomized, placebo-controlled trial would provide definitive evidence that reduction of PPIs use in haematological malignancy patients during and after chemotherapy is associated with a decreased risk of developing bacteraemia.

Conclusion

In conclusion, this study suggests a potential association between PPIs use and development of bacteraemia in haematological malignancy patients after chemotherapy. Reasons for PPIs use were inappropriate or undocumented in half of the patients. Caution is advised when considering the use of PPIs in haematological malignancy patients who have undergone chemotherapy. The use of prophylactic antibiotics would reduce the rate of gut-derived bacteraemia.

Disclaimer statements

Contributors None.

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Conflicts of interest There is no conflict of interest to report regarding this article.

Ethics approval This research has been approved by our Institutional Review Board.

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