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RISK OF SERIOUS INFECTION IN HEALTHCARE WORKERS WITH INFLAMMATORY BOWEL DISEASE: A CASE-CONTROL STUDY OF THE GROUPE D'ETUDE THÉRAPEUTIQUE DES AFFECTIONS INFLAMMATOIRES DU TUBE DIGESTIF (GETAID)

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SUMMARY

Background: Whether healthcare workers with inflammatory bowel disease (IBD) are at increased risk of severe infection due to daily pathogen exposure is controversial. Aim: To assess the risk of severe infection in healthcare workers with IBD in a large multicentre case-control study.

Methods: The study population comprised 482 healthcare workers with IBD from 17 centres who were matched for gender, age, disease subtype and year of diagnosis to 482 controls (non-healthcare workers with IBD). The study period was between the date of diagnosis of IBD and June 2016. Severe infection was defined as any community-acquired infection that required hospitalisation.

Results: With a median follow-up of 9.3 years, 139 severe infections were recorded among cases and controls, including 30 Clostridium difficile infections, 33 severe viral infections, nine tuberculosis infections, 21 community-acquired pneumonia and 46 others.

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No difference was observed between healthcare workers and controls regarding the overall incidence rates of severe infection. An increased risk of tuberculosis was noted in healthcare workers. In multivariate analysis in the entire study population, severe infection was associated with current exposure to corticosteroids (OR = 3.05,95% CI [2.06-4.52], $P < 0.001$), immunosuppressants (OR = 1.98, 95% CI [1.38-2.84], $P < 0.001$) and anti-TNF agents (OR = 2.93, 95% CI [2.024.27], $P < 0.001$) and reduced with Crohn's disease (OR = 0.63,95% CI [0.43-0.91], $P = 0.01$). Conclusions: Healthcare workers with IBD do not have an increased risk of severe infection compared with other patients with IBD, except for tuberculosis. Screening for tuberculosis exposure should be assessed in this high-risk population when treated with anti-TNF agents.

1. INTRODUCTION

The treatment methods for inflammatory bowel disease (IBD) have been dramatically altered by the advent of antitumour necrosis factor-α (TNF) agents within the last decades. In addition to a better control of the disease course resulting in fewer surgeries and, reduced need for hospitalisation and steroids, patients' lives have also improved resulting in better patient-related outcomes, quality of life, and work productivity.[1-3] Treatment strategies have then evolved with the establishment of new goals in the management of IBD especially for Crohn's disease and towards wider and earlier use of anti-TNF therapy and other biological agents alone and in combination with immunomodulators.[4,5]

This shift towards the step-up management paradigm has been counterbalanced by the infectious and neoplastic risks associated with conventional immunosuppressants and anti-TNF agents.[6,7] Therefore, the use of immunomodulator and/or biological agents based on infectious risk stratification is therefore questionable. Healthcare workers represent a subgroup of patients exposed to a substantial risk for acquiring incidental infection due to daily and close interactions with infected patients and asymptomatic carriers of pathogens. A retrospective study recently reported 20 incidental cases of pulmonary tuberculosis even though their initial screening test results were negative, including six healthcare workers.[8] We thus conducted a multicentre case-control study in a real-life setting with the aim to assess the incidence rate of severe infection in healthcare workers with IBD compared with other nonhealthcare worker patients with IBD, and to identify the associated predictors of severe infections.

2. MATERIALS AND METHODS

2.1. STUDY POPULATION

The present study was a retrospective observational multicentre casecontrol study conducted in 17

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French and Belgian academic centres affiliated with the Groupe d'Etude Thérapeutique des Affections Inflammatoires du tube Digestif (GETAID). From January 2015 to June 2016, investigators were asked to report consecutive patients with IBD followed up in their centre who were healthcare workers. Healthcare worker was categorised as physician, nurse, nurses' aide, or any other healthcare personnel interacting with in and out-patients.

Control patients were patients with IBD who were not healthcare workers. Control patients were recruited from the MICISTA registry, a tertiary monocentric clinical database of all consecutive patients with IBD at Saint-Antoine Hospital (Paris, France) to perform case-control matching on a large and exhaustive database without redundancy.[9,10]

Inclusion criteria included diagnosis of IBD according to European Crohn's and Colitis Organisation guidelines and age at diagnosis of IBD ≥18.[11,12] The protocol was both approved by the Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé (CCTIRS N°15.503) and the Commission Nationale de l'Informatique et des Libertés (CNIL N°916056). All authors had access to the study data and reviewed and approved the final manuscript.

2.2. DATA COLLECTION

Investigators from the participating centres were asked to complete a standardised questionnaire. An on-site visit was then conducted to collect missing data from the patients' case records. The date of inclusion corresponded to the date of diagnosis of IBD for cases and controls. At inclusion and until June 2016, the recorded data included a detailed account of the IBD diagnosis and history, smoking status, IBD phenotype according to the Montreal classification, medical and surgical treatment history and any serious infection history. For each of the patients, the disease duration was divided into semesters. For each semester, which was independently analysed, the occurrence of severe infection, smoking status, and immunosuppressive therapy (eg, steroids, thiopurines, methotrexate, anti-TNF therapy, ustekinumab, and anti-integrin therapy) were assessed.[13] A semester was considered as a treatment semester if the patient received steroids, immunomodulator and/or anti-integrin therapy during at least 3 months within the studied semester.

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From the diagnosis of IBD until June 2016 and for each patient, semesters in which healthcare workers did not work (training, sabbatical leave, retirement) and semesters after total proctocolectomy with ileal pouch-anal anastomosis in cases and controls with UC were not considered.

2.3. CASE-CONTROL STUDY

Controls were selected randomly within the MICISTA registry to match to the healthcare worker cases (one control for one case). MICISTA is an electronic database of the gastroenterology department of Saint-Antoine Hospital. All patients seen in the institution from 1994 are included in the database. Data regarding medical and IBD history and follow-up are prospectively coded in the system. Case-control matching was based on gender, birth year (± 2.5 years), type of IBD and IBD diagnosis calendar (± 2.5 years). Data collection was performed first from the MICISTA database and from the patients' case records in case of missing data.

2.4. OUTCOMES

The primary objective was to compare the overall incidence of severe infection in healthcare workers with IBD and controls. Severe infection was defined as any community-acquired infection that required hospitalisation including (a) *Clostridium difficile* infection (b) community-acquired pneumonia (c) *Mycobacterium tuberculosis* infection, (d) any other community-acquired infection that required hospitalisation. A specific case report form was used in case of severe infection. Patients were recruited from department's local databases and/or standardised hospital in-patient diagnostic dataset including ICD-10 codes.

The rates of overall severe infection and any specific severe infections were expressed for 100 patient-semester.

2.5. STATISTICAL ANALYSIS

Data were expressed as the means ± standard deviations or medians (interquartile range) in the case of continuous data. Nominal and ordinal data were compared using the Chi-square test or the Fischer's exact test as appropriate, whereas parametric data were compared using the Mann-Whitney tests and Wilcoxon's matched-pair signed-rank test as appropriate. Severe infection-free survival was calculated using the Kaplan-Meier method. For the comparison between semesters, an adjusted analysis according to the semester rank was performed to consider the influence of time (Mantel- Haenszel test). Factors associated with serious infection during a semester were first tested in univariate analysis: age, sex, IBD duration, IBD type (Crohn's disease or UC) and phenotype, familial history of IBD, smoking habit, extraintestinal manifestation of IBD, involvement, perianal disease, semester rank, healthcare worker, and IBD-related treatment (eg, steroids, immunomodulator, anti-TNF agent and, anti-integrin agents). Subsequent multivariate analyses using binary logistic regression models were

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performed separately for overall severe infection and specific severe infection and adjusted for the abovementioned variables with an ascending stepwise procedure using the Wald test. Quantitative values were converted to qualitative values using the dichotomy from the median value in two distinct groups of equal size. Variables with $P < 0.10$ in the univariate analysis were considered to be potential adjustment variables for the multivariate analysis. All analyses were two-tailed, and P values less than 0.05 were considered significant. All statistical evaluations were performed using SPSS statistical software (v17; SPSS Inc., Chicago, IL, USA). All authors had access to the study data and reviewed and approved the final manuscript.

3. RESULTS

3.1. STUDY POPULATION

In total, 482 healthcare workers with IBD were included: 335 (69.5%) with Crohn's disease, 136 (28.2%) with UC and 11 (2.3%) with IBDU. Patient demographic data, baseline diseases characteristics, and medication history are listed in Table 1. The healthcare worker is composed of 133 (27.6%) physicians, 158 (32.8%) nurses, 66 (13.7%) nurses' aides and 125 (25.9%) other healthcare professionals interacting with in and out-patients (Table S1).

Compared with nonhealthcare worker IBD controls, healthcare workers with IBD were characterised by a lower frequency of smoking (27.6% vs 48.5%, $P < 0.001$), and more frequent use of anti-TNF therapy (61.0% vs 53.3%, $P = 0.02$) (Table 1). A slight difference in the age at diagnosis was observed between healthcare workers with IBD and controls (27.3 $\pm$ 11.6 vs 26.9 $\pm$ 11.7 years, $P = 0.008$) which was consistent with matching criteria ($\pm$ 2.5 years). Healthcare workers with UC were more likely to exhibit pancolitis (60.0% vs 46.0%, $P = 0.02$). Healthcare workers with Crohn's disease were less likely to exhibit upper GI tract involvement (6.5% vs 12.9%, $P = 0.006$).

3.2. INCIDENTAL CASES OF SEVERE INFECTION

During the follow-up period, which was 9.3 [4.6-16.2] years, 22 477 semesters were analysed including 10 834 in the healthcare workers group and 11 643 in the control group. We collected 139 overall severe infections in 137 case and control patients accounting for an incidence rate of 0.61 $\pm$ 7.78 overall severe infections per 100 patient-semesters (Table 2). No deaths were noted in healthcare workers and the control group.

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No difference was noted between the healthcare workers and the control group regarding the incidence rate of overall severe infection (0.66 ± 8.13 vs 0.56 ± 7.45 per 100 patient-semesters, $P = 0.35$) (Table 2). The probabilities of developing severe infection in the entire study population were 1.0, 6.1%, 10.8%, and 14.1% at 1, 5, 10, and 15 years, respectively (Figure 1).

3.3. CHARACTERISTICS OF INCIDENTAL CASES OF SEVERE INFECTION

The 137 severe infections were diagnosed as follows: nine tuberculosis infections, 30 *Clostridium difficile* infections, 21 community acquired pneumonia infections, 33 severe viral infections, and 46 other severe infections requiring hospitalisation. Tuberculosis infection included two cases of pulmonary tuberculosis, one case of miliary tuberculosis, one case of pulmonary and hepatosplenic tuberculosis and five cases of primary tuberculosis infection. All cases of tuberculosis infection occurred in patients receiving an anti- TNF agent (9 out of 551 (1.6%) patients treated with anti-TNF agent) with a median delay of 16.0 [10.0-25.0] months. The five cases of primary tuberculosis infection were related to five healthcare workers with contacts of known tuberculosis patients with a negative positive interferon-gamma release assay before starting anti-TNF agent that became positive after contacts. The latter five patients were treated for primary tuberculosis infection with a 3 month course of isoniazide and rifampicine. Severe viral infections included 19 cases of *Cytomegalovirus* infection (18 primary infections and one reactivation), nine cases of severe *Epstein-Barr Virus* infection (nine primary infections and one reactivation, see Table S2), three cases of severe *Varicella zoster virus* infection (two chickenpox and one shingles) and two cases of severe *Herpes Simplex Virus* primary infection.

The other severe infections requiring hospitalisation included enteric infection in 18 cases (*Campylobacter* sp. infection in six cases, *Salmonella* sp. in one case, *Yersinia* sp. in one case, *Klebsiella oxytoca* in one case, and undocumented infection in eight cases), pyelonephritis in six cases, erysipelas in four cases, dental abscess in three cases, flu-like syndrome in three cases, sinusitis in three cases, sigmoid diverticulitis in two cases, catheter-related bloodstream infection in two cases, acute cholangitis in two cases, salpingitis in one case, acute cholecystitis in one case, and oesophageal candidiasis in one case.

No difference in any type of severe infection was noted between the healthcare workers and the control group with the exception of an increased risk of developing tuberculosis infection in the group of healthcare workers (0.07 ± 2.72 vs 0.009 ± 0.93 per 100 patient semesters, $P = 0.02$).

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TABLE 1. *Demographic and baseline disease characteristics and medication histories of 984 patients with inflammatory bowel disease including 482 healthcare workers*

Characteristic	Healthcare workers (n = 482)	Nonhealthcare workers (n = 482)	*P* value
Age at diagnosis, years	27.3 ± 11.6	26.9 ± 11.7	0.008
Male gender, no (%)	355 (73.7%)	356 (73,9%)	1.00
BMI, kg/m2	22.7 ± 4.9	22.0 ± 4.4	0.03
History of smoking habits, no (%)	133 (27.6%)	230 (48.5%)	<0.001
Follow-up period, years	11.9 ± 9.1	11.9 ± 8.8	0.69
Extraintestinal manifestation, no (%)	36 (7.5%)	49 (10.2%)	0.17
Age at diagnosis, no (%)			
A1: ≤16 years	32 (6.6%)	70 (14.5%)	<0.001
A2: 17-40 years	403 (83.6%)	346 (71.8%)	<0.001
A3: >40 years	47 (9.8%)	66 (13.7%)	0.07
Crohn's disease, no (%)	335 (69.5%)	331 (68.7%)	1.00
Disease location, no (%)			
Ileal	125 (36.8%)	138 (40.4%)	0.35
Colonic	86 (25.3%)	88 (25.7%)	0.93
Ileocolonic	128 (37.6%)	116 (33.9%)	0.34
Upper GI tract	22 (6.5%)	44 (12.9%)	0.006
Disease phenotype, no (%)			
Non-stricturing - Non-penetrating	184 (53.8%)	194 (56.6%)	0.47
Stricturing	84 (24.6%)	63 (18.4%)	0.06
Penetrating	74 (21.6%)	86 (25.1%)	0.32
Perianal disease, no (%)	106 (22.0%)	109 (22.6%)	0.88
Inflammatory bowel disease undetermined, no (%)	11 (2.3%)	15 (3.1%)	0.70
Ulcerative colitis, no (%)	136 (28.2%)	139 (28.8%)	0.89
Proctitis	23 (12.8%)	16 (11.5%)	0.86
Left-sided colitis	49 (27.2%)	59 (42.4%)	0.006
Pancolitis	108 (60.0%)	64 (46.0%)	0.02
History of intestinal resection, no (%)	133 (28.3%)	148 (30.7%)	0.44
History of IBD treatment, no (%)			
Immunosuppressant	341 (70.7%)	379 (78.6%)	0.06
Anti-TNF therapy	294 (61.0%)	257 (53.3%)	0.02
Anti-integrin therapy	24 (5.0%)	19 (3.9%)	0.53
Ustekinumab	20 (4.1%)	9 (1.9%)	0.06

BMI, body mass index; GI, gastrointestinal; IBD, inflammatory bowel disease. Variables are presented as n (%), mean ± standard deviation or median (interquartile range). P values are based on a two-sided chi-square test for all categorical variables and on Wilcoxon's matched-pair signed-rank test for all quantitative variables.

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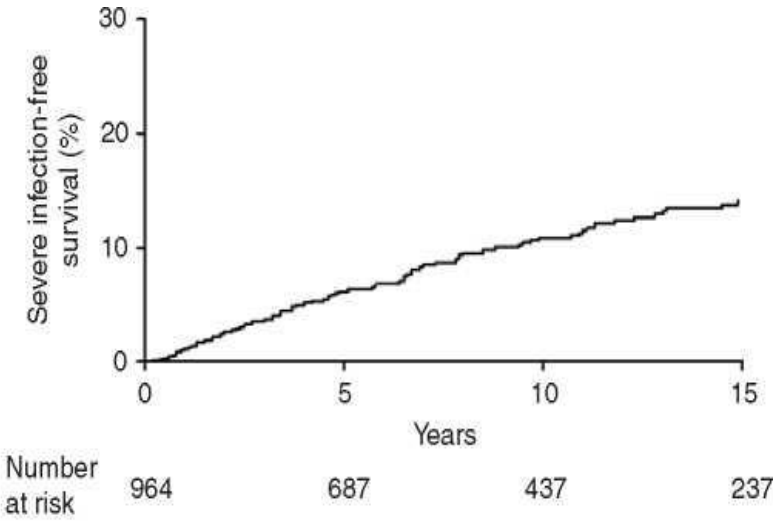
3.4. PREDICTORS OF SEVERE INFECTION

Predictors of overall severe infection were assessed in the entire study population including cases and controls, after dividing the follow-up period into semesters to take into account the impact of immunosuppressive therapy. In multivariate analysis, logistic regression analysis demonstrated that patients with steroids (OR = 3.05, 95% CI [2.064.52], $P < 0.001$), immunomodulators (OR = 1.98, 95% CI [1.38-2.84], $P < 0.001$), and anti-TNF therapy (OR = 2.93, 95% CI [2.02-4.27], $P < 0.001$) were more likely to develop severe infection (Table 3). Conversely, patients with Crohn's disease (OR = 0.63, 95% CI [0.430.91], $P = 0.01$) were less likely to develop severe infection.

Additional analyses demonstrated that physicians (OR = 8.00, 95% CI [1.01-62.50], $P = 0.05$), steroid therapy (OR = 6.17, 95% CI [1.56-24.39], $P = 0.009$), and anti-TNF therapy (OR = 4.62, 95% CI [1.18-18.18], $P = 0.03$) were associated with increased risks of developing tuberculosis infection. Patients with Crohn's disease (OR = 0.17, 95% CI [0.08-0.38], $P < 0.001$) and a BMI >20 kg/m^2 (OR = 0.44, 95% CI [0.20-0.94], $P = 0.03$) were less likely to develop *Clostridium difficile* infection whereas immunomodulators (OR = 2.58, 95% CI [1.19-5.59], $P = 0.02$) and anti-TNF therapy (OR = 2.88, 95% CI [1.32-6.29], $P = 0.001$) were associated with increased risks of developing *Clostridium difficile* infection.

Nurses and thiopurine therapy were associated with increased risks of developing severe viral infection. Patients aged >50 years (OR = 4.69, 95% CI [1.97-11.11], $P = 0.001$), anti-TNF therapy (OR = 5.1, 95% CI [2.14-12.20], $P < 0.001$), and vedolizumab therapy (OR = 23.81, 95% CI [3.03-200.00], $P < 0.001$) were associated with increased risks of developing community-acquired pneumonia.

FIGURE 1. *Kaplan-Meier curves of 984 patients with inflammatory bowel disease assessing the occurrence of incident cases of severe infection*



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4. DISCUSSION

In our study, we provide for the first time a case-control study assessing the risk of overall severe infection in patients with IBD according to professional exposure to pathogens. We did not identify any difference between healthcare workers and control patients with the exception of increased risks of developing tuberculosis infection in the healthcare workers group, especially in physicians. Predictors of any severe infection were related to immunosuppressive therapy, age and nutritional status with the exception of the risk of developing tuberculosis infection in physicians and severe viral infection in nurses.

Opportunistic infection remains a key safety concern in patients with IBD.[14] Opportunistic infection may be defined as serious infections by a micro-organism that has limited pathogenic capacity under ordinary circumstances such as parasitic or fungal infection, and infections that occur more frequently or are more severe in people with weakened immune systems.[14,15] In the present study, we chose to use the term of severe infection instead of opportunistic infection because we did not report any cases with rare severe infections, such as parasitic or fungal infections. Risk factors for developing opportunistic infection include immunosuppressive therapy (steroids ≥20 mg per day for ≥2 weeks and/or immunomodulator and/or biological agents), age, comorbidities, and malnutrition.[14] In the present study, we confirmed the impact of immunosuppressive therapy on the increased risk of severe infection. In contrast to a recent epidemiological study, we demonstrated that patients with Crohn's disease were less prone to develop severe infection.[16] Heterogeneity in colonic involvement between patients with Crohn's disease and UC may explain an increased propensity to develop *Clostridium difficile* infection in patients with Crohn's disease compared with patients with UC. Age was not a predictor of severe infection except for the risk of community-acquired pneumonia. However, it should be noted that the number of semesters in which patients were aged >60 years and >65 years were only 4.8% and 2.6%, respectively.

Exposure to pathogens and geographic clustering are considered as independent risk factor of opportunistic infection, prompting ECCO to recommend the avoidance of endemic areas by patients with IBD treated with immunosuppressive therapy.[14] In this setting, healthcare workers must be considered a population with a particular risk of opportunistic infection due to daily exposure to potential carriers of infectious agents that could be perceived as a contraindication to immunosuppressive therapy or a need for professional reorientation. In the present study, we did not demonstrate an increased risk of severe infection for healthcare workers with IBD as compared with controls. These data are reassuring for the daily management of such patients potentially considered at increased risk of exposure to infectious agents and may be extended to professions such as social workers or childcare workers.

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TABLE 2. *Incidence rates of opportunistic infection in 984 patients with inflammatory bowel disease based on healthcare worker status*

Characteristic	Healthcare personnel (n = 482)	Nonhealthcare personnel (n = 482)	Overall study population (n = 984)	*P* value
Any severe infection	72 events 0.66 ± 8.13	65 events 0.56 ± 7.45	137 events 0.61 ± 7.78	0.35
Tuberculosis	8 events 0.07 ± 2.72	1 events 0.009 ± 0.93	9 events 0.04 ± 2.00	0.02
Clostridium difficile infection	14 events 0.13 ± 3.59	16 events 0.14 ± 3.70	30 events 0.13 ± 3.65	0.99
Community-acquired pneumonia	8 events 0.07 ± 2.72	13 events 0.11 ± 3.34	21 events 0.09 ± 3.06	0.39
Severe viral infection	19 events 0.18 ± 4.18	14 events 0.12 ± 3.47	33 events 0.15 ± 3.83	0.30
Other opportunistic infection requiring hospitalisation	25 events 0.23 ± 4.80	21 events 0.18 ± 4.24	46 events 0.20 ± 4.52	0.46

Incidence rates are expressed as events per 100 patient-semesters.

TABLE 3. *The predictors associated with occurrence of severe infection in 984 patients with inflammatory bowel disease, including 482 healthcare workers*

	Any opportunistic infection		Tuberculosis		*Clostridium difficile* infection		Severe viral infection		Community-acquired pneumonia	
Variables	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Crohn's disease	0.63 [0.43-0.91]	0.01	-	-	0.17 [0.08-0.38]	<0.001	-	-	-	-
Age>50 years	-	-	-	-	-	-	-	-	4.69 [1.97-11.11]	0.001
Steroids	3.05 [2.06-4.52]	<0.001	6.17 [1.56-24.39]	0.009	-	-	-	-	-	-
Immunosuppressant	1.98 [1.38-2.84]	<0.001	-	-	2.58 [1.19-5.59]	0.02	-	-	-	-
Thiopurine	-	-	-	-	-	-	7.87 [3.55-17.54]	<0.001	-	-
Anti-TNF therapy	2.93 [2.02-4.27]	<0.001	4.65 [1.18-18.18]	0.03	2.88 [1.32-6.29]	0.001	-	-	5.1 [2.14-12.20]	<0.001
Anti-integrin	-	-	-	-	-	-	-	-	23.81 [3.03-	<0.001

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Physician	-	-	8.00 [1.01-62.50]	0.05	-	-	-	-				
BMI >20 kg/m²	-	-	-	-	0.44 [0.20-0.94]	0.03	-	-	-	-		
Nurse	-	-	-	-	-	-	2.15 [1.02-4.52]	0.04	-	-		

BMI, body mass index; CI, confidence interval; OR, odd ratio.

Anti-TNF therapy is associated with an increased risk of severe infection and more specifically of tuberculosis infection.[6,17-19] In the present study, we demonstrate that physicians with IBD exhibited an 8-fold increased risk of developing tuberculosis infection. Transmission of tuberculosis occurs through droplet nuclei aerosolised by patients with unrecognised or inappropriately treated tuberculosis.[20] Healthcare workers exhibit an increased risk of developing latent tuberculosis infection.[21] Indeed, since 1994, the *French* Code of Public Health has required *Bacille Calmette-Guerin* vaccination for all healthcare workers employed in public and private institutions, including students.[22] In patients with IBD travelling to areas where tuberculosis is moderately to highly endemic who are receiving immunosuppressive therapy, tuberculosis screening test should be performed immediately after returning and 8-10 weeks after returning.[14] Based on our results, we proposed performing tuberculosis screening tests in patients with IBD who are receiving immunomodulator therapy every 6 months, to systematically screen for any contact with patients potentially infected by tuberculosis and to treat incident cases of latent tuberculosis infection.[23,24] In this setting, interferon-gamma release assays have demonstrated fair agreement with the tuberculin skin test and provide useful information for patients with IBD.[25]

Clostridium difficile infection is a common complication in IBD.[26] In healthy patients, the pathogenesis of *Clostridium difficile* infection relies on disruption of the colonic microbiome equilibrium by antibiotic therapy.[27,28] In IBD, colonic dysbiosis and exposure to immunosuppressive therapy may allow *Clostridium difficile* infection to develop in the absence of any antibiotic therapy. Whether healthcare workers exhibit increased carriage of *Clostridium difficile* and are at increased risk for developing *Clostridium difficile* infection remain unclear.[29-34] In the present study, healthcare workers did not present an increased risk of *Clostridium difficile* infection. An increased risk of *Clostridium difficile* infection was noted in patients treated with immunomodulators and anti-TNF therapy. An increased risk of *Clostridium difficile* infection was also noticed in patients with ulcerative colitis and IBDU possibility due to the heterogeneity of colonic involvement.

Immunosuppressive therapy is often associated with subclinical reactivation of latent *Herpes viridae* infections such as *Cytomegalovirus* and *Epstein-Barr virus.*[35,36]

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On the other hand, infection occurring during immunosuppressive therapy could be associated with severe viral infection and even haemophagocytic lymphohistiocytosis, a rare but potentially life-threatening complication.[37-39] In the present study, healthcare workers did not exhibit an increased risk of developing severe viral infection. Conversely, patients treated with thiopurines and nurses exhibited an increased risk of developing severe viral infection. Systematic screening should be established before starting thiopurines especially in young males and nurses, to warrant severe primary infection.

Based on two large case-control studies, patients with IBD had increased risk of pneumonia.[40,41] In the present study, we demonstrated that an increased risk of pneumonia was associated with patients aged >50 years, and those treated with vedolizumab and anti-TNF. Age is a known risk for opportunistic infection. These data support a pre-emptive pneumococcal vaccination in patients with IBD, especially those aged >50 years. To the best of our knowledge, vedolizumab was not associated with an increased risk of infection.[42-45] However, vedolizumab is associated with a specific pattern of incidental infection involving the upper respiratory tract and nasopharyngeal airway.[46] We believe that patients treated with vedolizumab should also receive pneumococcal vaccination.

Although patients were recruited from department's local databases and/or standardised hospital in-patient diagnostic dataset, the retrospective nature of the data collection may be biased. To overcome this limitation, we decided to focus on severe infection meaning those that required hospitalisation. The results of such case-control study may also be impaired by recruitment bias. However, although healthcare workers were recruited from 17 academic GETAID centres, the controls were recruited from the Saint-Antoine Hospital MICISTA registry including 8599 patients with IBD to ensure a random, nonredundant and unbiased case-control matching on gender, birth year, type of IBD, and IBD diagnosis calendar. Finally, it is conceivable that our study may be underpowered to accurately assess the risk of severe infection in patients with IBD. Nevertheless, our results are close to those presented recently in a French nationwide population-based study.[47]

We concluded that healthcare workers with IBD did not exhibit an increased risk of severe infection compared with controls. Special attention should be given to healthcare workers with IBD treated with anti-TNF based on the potential benefit of periodical screening for latent tuberculosis infection. Patients with IBD treated with anti- TNF and vedolizumab, especially those aged >50 years, should receive pneumococcal vaccination. Further studies are warranted to better understand whether immunosuppressive therapy should be administered according to risk stratification based on pathogen exposure in professionals.

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Guarantor of the article: Aurelien Amiot.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section at the end of the article.

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APPENDIX 1

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APPENDIX 2

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