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Genetic risk factors for serious infections in inflammatory bowel diseases

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Abstract

Introduction—Immunosuppression, the cornerstone of management of Crohn’s disease (CD) and ulcerative colitis (UC) (inflammatory bowel diseases; IBD) is associated with an increased risk of serious infections that is inadequately predicted by clinical risk factors. The role of genetics in determining susceptibility to infections is unknown.

Methods—From a prospective consented patient registry, we identified IBD patients with serious infections requiring hospitalization. Analysis was performed to identify IBD-related and non-IBD related immune response loci on the Immunochip that were associated with serious infections and a genetic risk score (GRS) representing the cumulative burden of the identified SNPs was calculated. Multivariable logistic regression used to identify effect of clinical and genetic factors.

Results—The study included 1,333 IBD patients (795 CD, 538 UC) with median disease duration of 13 years. A total of 133 patients (10%) had a serious infection requiring hospitalization. Patients with infections were more likely to have CD and had shorter disease duration. The most common infections were skin and soft-tissue, respiratory, and urinary tract infections. Eight IBD risk loci and 2 other polymorphisms were significantly associated with serious infections. Each 1 point increase in the infection GRS was associated with a 50% increase in risk of infections (OR 1.53, 95% CI 1.37 – 1.70,) ($p=1\times 10^{-14}$), confirmed on multivariable

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analysis. Genetic risk factors improved performance of a model predicting infections over clinical covariates alone ($p < 0.001$).

Conclusions—Genetic risk factors may predict susceptibility to infections in patients with IBD.

Keywords

infections; genetics; Crohn's disease; pneumonia; sepsis; immunosuppression

INTRODUCTION

Over a quarter of all hospitalizations for inflammatory bowel diseases (IBD; Crohn's disease (CD), ulcerative colitis (UC)) are associated with infections^{1–6}. In addition to the associated morbidity, infection-related hospitalizations are associated with a five-fold increase in mortality when compared to those that do not occur in the context of infections^{7, 8}. An increase in risk of infections in patients with IBD is conferred by a spectrum of disease- and treatment-related factors^{1–6, 9}. Those pertaining to the patient include co-morbidity, severity of IBD, predisposing behavior such as perianal or internally penetrating CD, and malnutrition^{1, 2, 4–6, 10, 11}. Important in the context of IBD, systemic immunosuppression that remains the cornerstone of its management, confers a two-fold increase in risk of opportunistic and other serious infections^{2, 6, 9, 12}. In clinical trials and prospective observational cohorts, up to 10% of patients on immunosuppressive therapy may develop a significant infection, with 5% developing serious complications often requiring hospitalization^{11–14}. The use of systemic corticosteroids has been consistently associated with an increase in risk of infections, and such risk may act synergistically over and above that conferred by other immunosuppressive therapy⁹. The literature on the risk associated with conventional immunosuppressive (thiopurine, methotrexate) or anti-tumor necrosis factor- α (anti-TNF) biologic therapy is more mixed but a majority of data support a modest increase in risk, particularly for opportunistic infections^{2, 4–6, 9, 12}. Additionally, agent-specific risks may exist with distinct therapeutic classes such as re-activation of tuberculosis or hepatitis B with anti-TNF therapy¹⁵.

The key mechanism underlying the development of IBD is a dysregulated immune response to commensal microbial flora in a genetically susceptible host^{16, 17}. Central to this hypothesis is the recognition that many of the key genes involved in the pathogenesis of IBD such as *nucleotide-binding oligomerization domain containing 2* (*NOD2*), autophagy (*ATG16L1*), interleukin-23 (IL-23), *leucine-rich repeat kinase* (*LRRK2*), or major histocompatibility (MHC) class II antigens are critically important in pathogen sensing and mounting appropriate immune responses to ensure bacterial clearance^{16, 18}. Disruptions of the function of such genes result in inappropriate propagation of immune-responses. With this background, it is conceivable that polymorphisms in these genes could also confer susceptibility to significant infections occurring in patients with IBD. Prior gene-associations studies have not evaluated patients with IBD but have demonstrated an association between toll-like receptor 4 (*TLR4*) and cluster of differentiation 14 (*CD14*) polymorphisms and gram-negative infections^{19–21}, and *TLR2* polymorphisms and gram positive infections²⁰. An association study identifying genetic susceptibility to infections has not been broadly studied in the context of all serious infections occurring in IBD patients,

but would be particularly pertinent given predisposition conferred additionally by disease- and treatment-related factors.

Consequently, we performed this study to (1) identify genetic alleles that may confer susceptibility to serious infections in patients with IBD; and (2) to examine the added utility of such genetic factors over clinical variables in these patients.

METHODS

Study population

Patients included in the study were from a prospective consented patient registry at Massachusetts General Hospital (PRISM; a Prospective Registry for IBD Study at MGH). This is a prospective cohort recruiting adult patients 18 years and older with a diagnosis of CD, UC, or indeterminate colitis who are receiving care at the MGH Crohn's and Colitis center. Details about the registry have been described in detail in prior publications^{22–24}. In brief, after obtaining informed consent from patients with a definite diagnosis of IBD according to standard criteria²⁵, a detailed intake questionnaire is completed for each patient, assessing details about demographics, disease course, and current and past medical and surgical treatments. Age, gender, race, smoking status, and type of IBD are noted by a trained research coordinator. For patients with CD, disease location and behavior, and for those with UC, disease extent, was classified according to the Montreal classification²⁶.

Outcomes

The main outcome was an infection-related hospitalization. This was ascertained in two steps. First, we identified all potentially eligible patients by extracting those with at least one International Classification of Diseases, 9th edition, clinical modification (ICD-9-CM) code for an infection¹. From this list, chart review was performed for every patient by a study investigator (SS) under supervision of the senior investigator (AA) to confirm the diagnosis of an infection requiring hospitalization. We restricted this analysis to infections requiring hospitalization for two reasons. First, these are the most clinically consequential, contributing to significant morbidity, risk of mortality, and healthcare costs. Second, the accuracy of such diagnoses is higher and they are often supported by objective findings (positive microbiological cultures, radiographic findings) when compared to ambulatory infections where diagnosis is often made clinically and treatment is symptomatic. As IBD risk alleles may contribute to disease behavior and severity, we specifically excluded infections representing a severe manifestation of underlying IBD such as perianal abscess or an ileal phlegmon in those with CD. We excluded *Clostridium difficile* infections as these had previously been studied in another genetic-association study²⁷. Patients with HIV, organ transplant recipients, cancer patients undergoing chemotherapy, and patients with metastatic malignancies were excluded. For each infection, we noted site and type of infection, ongoing IBD-related medications at the time of the episode, predisposing factors, outcomes of the infection episode including requirement for intensive care unit (ICU) management, treatments administered and mortality. Infections were grouped together by organ system of involvement.

Genotyping

Each consented patient provided blood for extraction of the DNA for genotyping. Genomic DNA was extracted from the buffy coat as previously described^{23, 24} and genotyping was performed on the Illumina Immunochip as described at the Broad Institute (Cambridge, MA)²⁸. The Immunochip is a custom chip designed for deep replication of loci associated with autoimmune diseases and covers 196,524 distinct loci putatively associated with immune function and response.

Statistical Analysis

Genotype association analysis was performed using Plink (v 1.07)²⁹ while statistical analysis and multivariable modeling was performed using Stata 13.2 (StataCorp, College Station, TX). Continuous variables were summarized using means and standard deviations while categorical variables were expressed as proportions and compared using the chi-square test. For identification of clinically relevant covariates, we utilized logistic regression with the infection-related hospitalization as the outcome. Potentially relevant variables were defined as those with a p-value < 0.10 on univariate analysis. Genetic association analysis was performed using two thresholds. From among the 201 IBD risk alleles deemed *a priori* to be of greater biological plausibility³⁰, potentially relevant SNPs were defined as those with a p-value < 0.05. For the rest of the loci on the immunochip, a more rigorous threshold of $p < 1 \times 10^{-5}$ was applied to minimize false discovery. All SNPs met Hardy-Weinberg equilibrium p-value > 0.01, and call rate > 95%. The genotyping success rate was 98% for the 201 IBD risk SNPs and 91% for the rest of the SNPs on the Immunochip. All patients were Caucasians of European ancestry and none were family members. Sensitivity analysis adjusted further for ancestry using the first five elements of a principal component analysis. A genetic risk score (GRS) representing the cumulative burden of the identified infection-risk SNPs was calculated and modeled both as a continuous variable and in quartiles. Loci that were protective were assigned inverse weights in developing the GRS to ensure similar direction to all loci comprising the GRS score (i.e. loci that increase risk were assigned a 0, 1, and 2 for wild type, heterozygous, and homozygous, while protective loci were assigned as 2, 1, and 0, for wild type, heterozygous and homozygous states respectively). A multivariable logistic regression analysis was then performed incorporating both clinically relevant variables as well as the GRS. The relative contribution of the clinical and genetic variables was quantified by comparing the area under the receiver operating characteristics (ROC) curve and likelihood ratio tests. The final multivariable model identified significant variables with a p-value < 0.05. Internal validation was performed by bootstrapping with 10,000 replications. The study was approved by the Institutional Review Board of Partners Healthcare.

RESULTS

Study Population

This study included 1,333 patients with IBD (795 CD, 538 UC). The median age at diagnosis was 25 years, and disease duration was 13 years. Just under half (46%) of the cohort were male, and median age at inclusion in the study was 42 years. Approximately one third of the patients were current users of systemic steroids (33%), immunomodulators

(30%), or anti-TNF biologics (infliximab, adalimumab, certolizumab pegol, golimumab) (29%). A total of 133 patients acquired infections prompting hospital admission or extending their hospitalization. Table 1 compares baseline characteristics of those with infections to patients with an infectious complication. Patients with an infection-related hospitalization were similar in age (45 vs. 43 years, $p=0.18$), and gender to those without an infection. However, they tended to have slightly shorter disease duration (14 years vs. 16 years, $p=0.009$) and were more likely to have penetrating behavior of CD (45% vs. 29%, $p=0.001$). The occurrence of infections was similar across all locations of CD and whether there was pancolonic involvement in UC. There was no difference in proportion of patients who were current users of corticosteroids (36% vs. 33%), immunomodulators (32% vs. 30%), or anti-TNF biologics (26% vs. 29%) ($p > 0.4$ for all).

The most common infections were skin and soft-tissue infections ($n=38$), respiratory tract infections including pneumonia ($n=26$), viral infections ($n=28$), and urinary and gynecologic infections ($n=35$) (Figure 1). Bacteremia occurred in 18 patients while 11 patients had opportunistic infections (candidal esophagitis, histoplasmosis, and pneumocystis jirovecii pneumonia). In terms of illness severity, 29 patients showed evidence of sepsis and 13 required admission to the ICU. All but 5 patients received treatment with systemic antibiotics. None of the infections resulted in mortality.

Genetic association analysis

Eight IBD risk loci and two additional loci on the immunochip met our *a priori* defined threshold for statistical significance (Table 2). The most likely candidate genes for each of the loci are listed in Table 2 and include several that may influence immune response to pathogens including *SLC10A4* on chromosome 4 ($p=0.01$), chemokine ligands (*CXCL1, 2, 3, 5 and 6*), interleukin-8 (IL-8) ($p=0.002$), *IFN- γ* and *IL-22* ($p=0.02$), and nitric oxide synthase (*NOS2*) ($p=0.04$). Three loci were associated with an increased likelihood while the remaining polymorphisms were inversely associated with risk of infection. On univariate analysis, each 1 point increase in a GRS comprising these 10 alleles was associated with a 50% increase in risk for infections (Odds ratio (OR) 1.53, 95% confidence interval (CI) 1.37 – 1.70, $p=1 \times 10^{-14}$). This remained unchanged on adjustment for ancestry using the first five elements of the principal component analysis (OR 1.52, $p=4 \times 10^{-14}$). Dividing the GRS into quartiles, patients in the fourth quartile had an eight-fold increase in risk of infections compared to the lowest quartile (OR 8.69, 95% CI 4.32 – 17.49, $p=1 \times 10^{-9}$) (Figure 2). Repeating the analysis with a GRS that weighted for the odds ratio for strength of association with infections yielded similar findings (OR 1.42 for each 1 point increase in GRS, $p < 0.00001$).

Multivariable analysis

On a multivariable analysis including age, type of IBD, disease duration, medication use and the GRS, a diagnosis of CD (vs. UC) (OR 1.81, 95% CI 1.19 – 2.75), disease duration (OR 0.98, 95% CI 0.96 – 0.99) and infection GRS (OR 1.50, 95% CI 1.35 – 1.68, $p=1 \times 10^{-13}$) were independent predictors of an infection-related hospitalization with an area under the curve of 0.71 (Table 3). A model incorporating the GRS performed significantly better than one including clinical data alone (AUROC 0.62, $p < 0.0001$) suggesting significant

incremental value to genetics in predicting infections in our IBD cohort. Our findings were robust on bootstrapping with 10,000 replications. Analysis stratified by IBD type yielded similar magnitude of effect in both CD (OR 1.57) and UC (OR 1.51). Penetrating disease phenotype was associated with a two fold increase in risk of infections in CD (OR 2.38, 95% CI 1.43 – 3.98). However, the effect of the genetic risk score was independent of disease phenotype and did not itself predict the occurrence of penetrating complications ($p=0.26$).

Subgroup analysis by type of infection revealed a similar strength of association with pneumonia, skin and soft-tissue infections, bacteremia, viral infections, post-operative infections, and opportunistic infections (Table 4). Analysis stratified by use of steroids, immunosuppression, or anti-TNF use revealed similar strengths of association among users and non-users of each therapy class. Each 1 point increase in the infection GRS was associated with a similar increase in risk of infections in patients on immunosuppression (OR 1.51, $p=8 \times 10^{-10}$) as in those not on any immunosuppression (OR 1.55, $p=4 \times 10^{-6}$).

DISCUSSION

Infections are an important concern in the management of patients with IBD and are influenced by both patient characteristics and treatment-related immunosuppression. Despite recognition of several risk factors for such infectious complications, they remain largely difficult to predict as most individuals with a risk factor will not develop an infectious complication but will have a significant benefit from immunosuppressive treatment^{2, 4-6, 9}. In this study, using a large, well characterized cohort, we demonstrate a novel association between several genetic risk alleles and risk of infection-related hospitalizations in patients with IBD. Each one point increase in our GRS predicting susceptibility to such serious infections was associated with a 50% increase in odds of an infection-related hospitalization. Further this association was noted independent of and contributed additionally to the ability to predict infections over clinical covariates. We identified similar associations across a spectrum of infections, and independent of ongoing immunosuppressive therapy suggesting that the polymorphisms identified may be broadly systemic in their immunologic effect and not influence immune response pertaining to a single organ system or microbial pathogen alone.

Several of the potentially relevant genes identified in our association analysis including IFN- γ , IL-8, IL-22, and chemokine ligands have been well described in the context of their influence on immune function and response to microbial pathogens. The chemokine ligands, in particular CXCL 1, CXCL3, and CXCL 5 act as potent chemoattractants for neutrophils³¹⁻³⁴. Leukocyte chemotaxis is important for microbial clearance, but can also lead to organ injury and complications when immune cell recruitment is dysregulated. In animal models, the chemokine receptor CXCL10 was essential to promote immunity against respiratory syncytial virus³³ while *CXCL1* was important in regulating pulmonary immune response to *Klebsiella pneumoniae*. Inhibition of *CXCL1* function was associated with reduced neutrophil migration to an *Escherichia coli* challenge and transgenic mice over expressing CXCL1 demonstrated lower systemic bacterial burden following a *K pneumoniae* challenge³². IFN- γ activates a wide range of immunocompetent cell types, including macrophages, endothelial cells, and lymphocytes, and is a key factor for the expression of

class II MHC molecules on antigen presenting cells^{35–39}. It also decreases epithelial barrier function and promotes neutrophil migration by increasing expression of chemokines and their receptors^{38, 39}. Mucosal IFN- γ levels are increased in experimental models of colitis and human IBD^{35, 37, 38}. IFN- γ is critical for immune response to infections, in particular viral infections, mycobacterial infections, and intracellular pathogens^{40, 41}. IL22 and IL26 are also important in mediating susceptibility to and recovery from human viral infections including influenza A and bacterial pathogens^{42, 43}. NOS2 has been demonstrated to play a role in murine cytomegalovirus and Cocksackie virus infections^{44, 45}. In addition to their direct role in immune responses, polymorphisms at these loci may also influence the response to infectious agents through pathways that are activated downstream such as the STAT1/3 pathways, both of which are activated by IL22 and IL26 and induce expression of TNF α , IL8, IL10, and ICAM-1⁴⁶. The Nicotinamide mononucleotide (NMN) adenylyltransferase 2 (Nmnat2) is an enzyme expressed primarily in the brain that catalyzes synthesis of NAD from nicotinamide mononucleotide and ATP. While its role in maintain neuronal integrity has been well described⁴⁷, its exact immunologic role in mediated infections is unknown.

Prior models for predicting infections in IBD focused on patient characteristics and treatments. A particularly consistent culprit has been use of systemic corticosteroids^{2–5, 9}. Pooled analyses from 71 clinical trials across various diseases demonstrated a 60% increase in risk of infections with corticosteroid use at a dose higher than 10mg/day⁴⁸. Similar results have been demonstrated from observational cohorts and registries; an analysis of the Crohn's Therapy, Resource, Evaluation, and Assessment Tool (TREAT) registry suggested a 2-fold increase in risk of infections steroid use⁴. The literature on the risk associated with immunomodulator or anti-TNF biologic therapy is more mixed. In patients with rheumatoid arthritis, no increase in risk of infections was noted with methotrexate⁴⁹. No statistically significant increase in risk was noted among thiopurine users compared to non-users in the TREAT registry⁴. A meta-analysis of risk of infection with anti-TNF biologic therapy revealed a weak increase in risk of any infections with statistical significance attained only for opportunistic infections but not serious infections, which in contrast, actually demonstrated a trend towards a lower frequency in biologic users compared to controls¹². In a multi-source administrative cohort, Grijalva identified no increase in risk of infection-related hospitalizations with anti-TNF therapy compared to non-users¹³. Consistent with some of these prior studies, we observed no statistically significant increase in risk of infection-related hospitalizations in our cohort with use of immunomodulators or anti-TNF agents. There are few possible explanations for a lack of association with corticosteroid use in our cohort. First, given the relatively infrequent nature of serious infections requiring hospitalizations, our cohort may have lacked the statistical power to identify such an association. Second, it is possible that the infection risk is determined by dose and duration of corticosteroid use; we were not able to account for these parameters in our analysis. Third, by virtue of our setting in a tertiary referral center, the greater baseline severity of disease in our cohort may have contributed to more homogeneity in risk of severe infections than observed in population-based cohorts.

There are several implications to our findings. To our knowledge, ours is the first study examining an association between genetic polymorphisms in genes mediating immune

responses and risk of infection-related hospitalizations in IBD. Each individual SNP identified and the cumulative GRS conferred broad susceptibility to (or protection from) a spectrum of infectious complications and was not organ- or microbial pathogen-specific. However, while there was a statistically significant incremental benefit to genetics over clinical risk factors alone, the overall ability to predict infections remained modest with an AUC of 0.71. Thus, infections, and in particular, serious infections remain difficult to predict in IBD patients and further study in larger cohorts is essential. While this modest performance precludes widespread use of such genetics based panels in the general IBD population at this time, in those considered particularly at high risk for a serious infection such as the elderly with significant comorbidity, even the modest improvement in ability to predict serious infections may be useful in determining the comparative benefits and competing risks of different therapeutic classes as well as between continued medical or surgical therapy. Prior to such adoption, functional studies examining the immune consequences of the relevant SNPs identified, particularly in responses to common infectious pathogens, are essential to provide mechanistic validation to our findings. These findings add insight into the role of immune-responses to microbial pathogens in the etiopathogenesis of IBD.

We readily acknowledge several limitations to our study. First, while our findings were robust on interval validation, external validation in other cohorts is essential, particularly in prospective cohorts where risk factors for infectious complications can be detailed accurately. Second, despite being the largest study of its kind thus far, the numbers of patients with infections by specific organ system or pathogen were low in our study. Thus, we lacked adequate statistical power to identify clinical and genetic risk factors specific to each infection subtype. Third, we restricted our outcome to infection-related hospitalizations. Thus, our findings may not be applicable to milder infections in IBD. Fourth, we were not able to account for all clinical risk factors such as dose or duration of exposure to systemic corticosteroid therapy or immunomodulator agents. With its setting in a tertiary referral center, the severity of illness of our IBD patients may be greater and our findings less generalizable to a broader population-based cohort. In this hypothesis generating study, we selected a lower threshold for identification of potentially relevant SNPs in the absence of robust preliminary data to inform this question. It is essential to both validate our findings in external datasets and, with accrual of larger cohorts, apply more conservative cut-offs to identify potential genes of interest that may influence risk of infections. The immunochip, by its design, would also bias towards identification of loci that may be more likely to influence immune response.

In conclusion, we demonstrate that genetic risk factors may influence susceptibility to serious infections in patients with IBD. Further validation and mechanistic studies are essential to confirm these findings. Upon availability of such data, it is conceivable that genetic information could be used to guide therapeutic choices to optimize patient outcomes by minimizing risk of serious adverse events related to therapy.

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Figure 1.
Distribution of various infection-related hospitalizations in a cohort of patients with inflammatory bowel disease

Figure 2.
Association between genetic risk score burden and risk of serious infections in inflammatory bowel diseases

Table 1

Characteristics of patients with inflammatory bowel diseases included in the study

Characteristic	With Infection (n= 133)	Without infection (n = 1,200)	P value
Mean age in years (SD)	42.9 (16.4)	44.7 (14.7)	0.19
Mean age at diagnosis	29.1 (15.5)	28.4 (13.2)	0.57
Male	44	47	0.53
Ever smoker	35	36	0.95
Disease duration	14.0 (13.7)	16.6 (10.4)	0.009
IBD type – Crohns	72	58	0.002
Disease location			
Ileal			0.84
Colonic	19 %	21 %	
Ileocolonic	22 %	25 %	
Upper GI	51 %	48 %	
involvement	8 %	6 %	
Disease behavior (CD)			0.001
Inflammatory	31 %	50 %	
Stricturing	24 %	21 %	
Penetrating	45 %	29 %	
Perianal involvement (CD)	33 %	28 %	0.29
Disease extent (UC) Pancolitis	59 %	53 %	0.59
Medication use			
Steroids	36 %	33 %	0.47
Immunomodulators	32 %	30 %	0.58
Anti-TNF agents	26 %	29 %	0.49

Anti-TNF – monoclonal antibodies to tumor necrosis factor α ; CD – Crohn's disease, UC – ulcerative colitis

Genetic polymorphisms associated with serious infections in patients with inflammatory bowel diseases

Table 2

Chromosome	SNP	Risk allele	Frequency affected	Frequency unaffected	P-value	Odds ratio	Potentially associated genes
1	rs10797879*	T	.37	.24	2.3e-06	1.89	NMNAT2 (NAD2)
3	rs4857658*	G	.18	.09	8.9e-06	2.14	
4	rs7438704	A	.29	.37	.01026	.69	TXK,TEC,SLC10A4
4	rs2457996	C	.17	.10	.002097	1.72	CXCL5,CXCL1,CXCL3,IL8,CXCL6,PF4,CXCL2,PF4V1
5	rs10061469	C	.25	.32	.02023	.71	
10	rs1250546	G	.31	.37	.04477	.76	ZMIZ1 (zinc finger)
12	rs7134599	A	.32	.39	.02843	.74	IFNG,IL26,IL22
13	rs17085007	C	.13	.20	.009851	.61	
17	rs2945412	G	.35	.41	.04018	.76	LGALS9,NOS2
18	rs7236492	T	0.16	0.12	0.0462	1.42	NEATC1

* Not IBD risk alleles

SNP—single nucleotide polymorphism

Table 3

Multivariable analysis of relevant clinical and genetic risk factors on susceptibility to infections

Characteristic	Odds ratio	95% confidence interval	P value
Crohn's disease	1.81	1.19 – 2.75	0.005
Disease duration	0.98	0.96 – 0.99	0.033
Infection GRS	1.50	1.35 – 1.68	1×10^{-13}

Table 4

Subgroup analysis of association between genetic risk score and susceptibility to the major organ-specific infections

Subgroup analysis	Odds ratio *	95% confidence interval	P value
Pneumonia	1.56	1.25 – 1.94	< 0.001
Soft tissue infection	1.39	1.15 – 1.67	< 0.001
Bacteremia	1.50	1.25 – 1.79	< 0.001
Viral infection	1.45	1.18 – 1.80	< 0.001
Opportunistic infections	1.67	1.19 – 2.33	0.003
Post op infection	1.47	1.24 – 1.74	< 0.001

* For each 1 point increase in the cumulative genetic risk score