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Research Article

Infections in Patients with Inflammatory Bowel Disease: A 30-Year Experience

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Abstract

Background: There is a broad spectrum of infections that may occur in IBD. The aim of the present study was to explore infections in IBD patients monitored for the past 30 years.

Materials and Methods: A total of 527 IBD patients of the University Gastroenterology Dept. and the associated Gastroenterology Outpatient Clinic were scrutinized between 1982 - 2012. The SPSS25 software was used for the statistical analysis; Mean and median values and standard deviations were estimated and used for the description of quantitative variables. Absolute (n) and relative (%) variables were used for the description of qualitative variables.

Results: The average age of diagnosis was 23.2 (± 9.3) years. Among the 527 IBD cases that were examined, 42.7% (n = 225) developed an infection, and the most common cause of the infection was a microbial factor in 38.7% of the CD patients and in 42% of the UC patients. From total patient sample, 39.6% had to be admitted to the hospital in order for their infection to be properly treated, with an average hospital stay of 11.1 ± 9 days, while in case of a gastrointestinal associated infection, the hospital stay duration increased in average by 3 days (13.63 ± 3.41).

Conclusions: The occurrence of infections in IBD patients is quite common, and it could be the product of several factors, such as the patient's age, their treatment, comorbidities and various other factors that alter the final result and make each case different.

Keywords: *Infections; IBD; Clostridium difficile; Immunosuppression*

Abbreviations

IBD: Inflammatory Bowel Disease; CD: Crohn's Disease; UC: Ulcerative Colitis

Introduction

IBD is a condition directly linked to infectious factors and infections regarding both its etiopathogenesis and its evolving clinical course [1-3]. The European Crohn's and Colitis Organisation (ECCO), after a consensus panel suggested that IBD patients should not be a priori considered to be in immunosuppression [4]. Nevertheless, IBD treatment calls for long-term use of corticosteroids, immunomodulating and biological agents, and can consequently provide the basis for the development of various infections [5]. Of course, there are many other factors that can affect the development of an infection, such as gender, age, type of disease or treatment, level of vaccination coverage and comorbidities [6-8]. Advanced age is the most common factor for infection development in IBD patients; in fact, the relative risk is 1.5 times greater in older patients compared to younger ones [9,11]. There is a broad spectrum of infections that may occur in IBD and there is also a higher risk of tuberculosis in IBD patients, especially those under treatment with Infliximab or other immunomodulating agents [12-14].

Aim of the Study

The aim of the present study was to explore infections in IBD patients monitored for the past 30 years.

Materials and Methods

In this study we included patients treated in the University Gastroenterology Department of the General University Hospital of Ioannina, Greece, the 1st Internal Medicine Dept. of the General University Hospital of Ioannina, the "G. Hadjicostas" General Hospital of Ioannina, and gastroenterologists of the District between 1982 - 2012.

It is a retrospective study through the records of the University Gastroenterology Dept. of the General University Hospital of Ioannina. A total of 527 IBD patients of the University Gastroenterology Dept. and the associated Gastroenterology Outpatient Clinic were scrutinized. Anonymity and confidentiality of the patients were strictly observed (Figure 1).

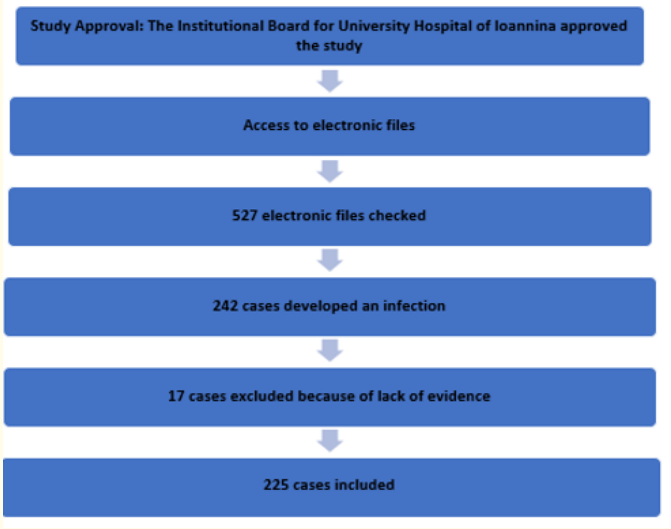

Figure 1: *Flowchart of the study.*

Ethics

Anonymity and confidentiality regarding the patients' data was observed.

Statistical analysis

The SPSS 25 software was used for the statistical analysis. Mean and median values and standard deviations were estimated and used for the description of quantitative variables. Absolute (n) and relative (%) variables were used for the description of qualitative variables.

Results

The majority of the patients were male (59.6%) and the females made up the remaining 40.4%. Regarding the diagnosis, 61.6% of the patients had UC, 34.4% suffered from CD and the remaining 4% had some type of *Indeterminate Colitis (IC)*. The average age of diagnosis was 23.2 (± 9.3) years.

It was found that 39.6% of the patients had also IBD with an average duration between 21 - 30 years, 30.6% of them had an average duration of 11- 20 years, 18.9% of them with a duration between 31 - 40 years, 8.1% of the patients with less than 10 years, and 2.7% of the patients with more than 41 years. 97.7% of the patients were alive at the time of the investigation, while 2.3% had passed away. One patient had died because of septicaemia due to microbial infection. In UC patients the distribution was as follows: 48.2% had pancolitis and 49.6% had left sided colitis, whereas in CD patients, 39.3% had colitis and 20.2% had ileitis (Table 1).

Ulcerative Colitis		Disease	
		Crohn's Disease	
Pancolitis	n	68	0
	%	48.2%	0.0%
Left-sided colitis	n	70	0
	%	49.6%	0.0%
Proctitis	n	3	0
	%	2.1%	0.0%
Colitis	n	0	33
	%	0.0%	39.3%
Ileitis	n	0	17
	%	0.0%	20.2%
Ileocolitis	n	0	11
	%	0.0%	13.1%
Other	n	0	23
	%	0.0%	27.4%

Table 1: *Type of disease and localization.*

Among the 527 IBD cases that were examined, 42.7% (n = 225) developed an infection, and the most common cause of the infection was a microbial factor in 38.7% of the CD patients and in 42% of the UC patients. Viruses, fungi, parasites caused an infection at lower levels, 25.2%, 7.6%, and 1.5% respectively in CD patients and 26.7%, 5.3% and 1.3% in UC patients respectively; there was no statistically important difference among the cause of the infection and the respective disease (p = 0.652), while in 23.7% of UC patients and 28% of CD patients the microbial factor remained unidentified (Figure 2).

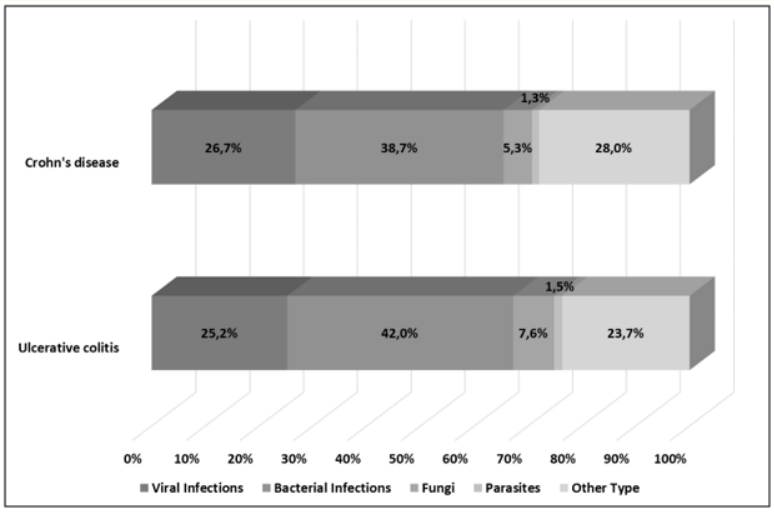

Figure 2: *Possible Cause of Infection.*

In 40.7% of UC patients and 44.2% of CD patients the duration of the disease was between 21 - 30 years, while in 44.4% of the patients with IC the duration was 11 - 20 years (Table 2).

< 10		**Years of diagnosis**				
		11 - 20	**21 - 30**	**31 - 40**	**41<**	
Ulcerative colitis	N	10	29	55	36	5
	%	55.6%	43.3%	62.5%	85.7%	83.3%
Crohn's disease	N	8	34	30	4	1
	%	44.4%	50.7%	34.1%	9.5%	16.7%
Indeterminate Colitis	N	0	4	3	2	0
	%	0.0%	6.0%	3.4%	4.8%	0.0%

Table 2: *Years of diagnosis per disease.*

Half of the patients (51.1%) developed an infection just once, 22.6% of them twice, 15.6% three times and 10.9% of them four times or more. Patients with UC had had more infections than patients with CD and IC, although this finding was of no statistical importance (57% vs 42.1% vs 33.3%, p = 0.149). Regarding the localization of the infection, in 98.2% of the patients it affected their gastrointestinal system, in 38.3% it affected the skin, in 27.7% the higher respiratory system and in 16.8% the urinary system.

Regarding the underlying cause, most of the viral infections affected higher and lower respiratory system, the genital system and could cause viremia, while microbial infections usually affected the gastrointestinal and the urinary system. Especially 45.9% of the cases where the gastrointestinal system was affected were caused by microbial factors. In total, 56.62% of the cases had suffered a major infection (Table 3).

Viral		Possible cause of infection				
		Microbial	Fungi	Parasites	Other	
Higher respiratory	N	26	3	0	0	5
	%	76.5%	8.8%	0.0%	0.0%	14.7%
Lower respiratory	N	7	4	0	0	5
	%	43.8%	25.0%	0.0%	0.0%	31.3%
Gastrointestinal	N	48	134	9	5	96
	%	16.4%	45.9%	3.1%	1.7%	32.9%
Urinary	N	1	16	1	0	4
	%	4.5%	72.7%	4.5%	0.0%	18.2%
Hepatobiliary	N	2	1	0	0	3
	%	33.3%	16.7%	0.0%	0.0%	50.0%
Cns	N	2	2	0	0	6
	%	20.0%	20.0%	0.0%	0.0%	60.0%
Reproductive	N	5	0	2	0	0
	%	71.4%	0.0%	28.6%	0.0%	0.0%
Skin	N	6	11	15	1	5
	%	15.8%	28.9%	39.5%	2.6%	13.2%
Pancreas	N	1	0	0	0	2
	%	33.3%	0.0%	0.0%	0.0%	66.7%
Blood	N	8	6	0	0	1
	%	53.3%	40.0%	0.0%	0.0%	6.7%
Eyes	N	1	1	0	0	3
	%	20.0%	20.0%	0.0%	0.0%	60.0%
Teeth	N	1	0	0	0	1
	%	50.0%	0.0%	0.0%	0.0%	50.0%

Table 3: *Possible cause of infection compared to the system affected by the infection.*

Severity of Infection fever, severe clinical condition, laboratory-confirmed infection.*

From the total patient sample, 39.6% had to be admitted to the hospital in order for their infection to be properly treated, with an average hospital stay of 11,1 ± 9 days, while in case of a gastrointestinal associated infection, the hospital stay duration increased in average by 3 days (13.63 ± 3.41) (Table 4).

Regarding IBD treatment, the majority of the sample received cortisone (45%), mesalazine (42.2%), azathioprine (21.6%) and sulfasalazine (21.4%), with fewer reporting taking some other treatment. Only 14.9% received infliximab and 3.9% adalimumab as the main IBD treatment. An important finding was that 58.4% of the patients after the infection had to have their treatment regimen changed or modified.

In-hospital		Type of treatment	
		Out of hospital treatment	
Ulcerative colitis	n	81	56
	%	59.1%	40.9%
Crohn's Disease	n	48	28
	%	63.2%	36.8%
Indeterminate colitis	n	7	2
	%	77.8%	22.2%

Table 4: *Main Type of Treatment per Disease.*

No statistically significant difference was found between the risk of infection and the type of treatment (mesalazine, methotrexate, infliximab, adalimumab, other medicine, cortisone, sulfalazine -p = 0.125 p = 0.336, p = 0.424, p = 0.614, p = 0.871, p = 0.667, p = 0.130, respectively), but there was a positive correlation between treatment with azathioprine and risk of viral infection (29.6%, p = 0.031). Among the patients receiving mesalazine, 37.5% was affected by an infection once, 29.3% of the patients receiving azathioprine had had an infection twice, 41.7% of those receiving methotrexate were affected four times, as were 40% of those receiving infliximab with statistical significance (p = 0.001, p = 0.001, p = 0.006, p = 0.002, respectively) (Table 5).

Mesalazine 1 time		Number of Infections				P value
		2 times	3 times	4+ times		
No	n	68	20	3	10	0.001
	%	67.3%	19.8%	3.0%	9.9%	
Yes	n	45	30	21	24	
	%	37.5%	25.0%	17.5%	20.0%	
Azathioprine 1 time		**Number of Infections**				**P value**
		2 times	**3 times**	**4+ times**		
No	n	99	33	11	20	0.001
	%	60.7%	20.2%	6.7%	12.3%	
Yes	n	14	17	13	14	
	%	24.1%	29.3%	22.4%	24.1%	
Methotrexate 1 time		**Number of Infections**				**P value**
		2 times	**3 times**	**4+ times**		
No	n	112	47	21	29	0.006
	%	53.6%	22.5%	10.0%	13.9%	
Yes	n	1	3	3	5	
	%	8.3%	25.0%	25.0%	41.7%	

Infliximab 1 time		Number of Infections				P value
		2 times	3 times	4+ times		
No	n	112	45	21	28	0.002
	%	54.4%	21.8%	10.2%	13.6%	
Yes	n	1	5	3	6	
	%	6.7%	33.3%	20.0%	40.0%	
Adalimumab 1 time		**Number of Infections**				**P value**
		2 times	**3 times**	**4+ times**		
No	n	111	50	22	32	0.115
	%	51.6%	23.3%	10.2%	14.9%	
Yes	n	2	0	2	2	
	%	33.3%	0.0%	33.3%	33.3%	
Other 1 time		**Number of Infections**				**P value**
		2 times	**3 times**	**4+ times**		
No	n	111	46	23	32	0.285
	%	52.4%	21.7%	10.8%	15.1%	
Yes	n	2	4	1	2	
	%	22.2%	44.4%	11.1%	22.2%	
Cortisone 1 time		**Number of Infections**				**P value**
		2 times	**3 times**	**4+ times**		
No	n	81	22	4	7	0.001
	%	71.1%	19.3%	3.5%	6.1%	
Yes	n	32	28	20	27	
	%	29.9%	26.2%	18.7%	25.2%	
Sulfasalazine 1 time		**Number of Infections**				**P value**
		2 times	**3 times**	**4+ times**		
No	n	88	40	13	21	0.027
	%	54.3%	24.7%	8.0%	13.0%	
Yes	n	25	10	11	13	
	%	42.4%	16.9%	18.6%	22.0%	

Table 5: *Number of Infections and pharmaceutical treatment.*

Among the patients, 4.9% were affected with tuberculosis (TB). More specifically, from the 7 patients affected, all 7 had had positive Mantoux skin test results without Interferon-Gamma Release Assays (IGRAs) results, while 6 had had negative chest x-rays and only one patient had had a positive chest x-ray. Those patients' initial treatment was as follows: 4 of them received mesalazine and cortisone, 2 patients received azathioprine, infliximab, cortisone and 1 patient methotrexate.

Discussion

IBD is a special medical condition that has been under scrutiny by the medical community in the past 30 years. The patients are nowadays thoroughly monitored by specialized medical units that provide individualized services aiming at keeping the symptoms at low intensity and avoiding complications. Record-keeping of infections can yield valuable input to the scientific community and help medical practitioners evaluate and adjust the best treatment for their IBD patients [15]. The present study is a long-term, systematic and detailed record of patients who were monitored not strictly for IBD but for infections as well.

From all the patients that has had an infection (n = 225), the majority were 60 years old or older. Almost double the patients had been diagnosed with UC compared to those with CD, while there was a small percentage of patients with IC. For the most part, the disease had been diagnosed and monitored for 20 - 30 years, which makes this study more robust, since the patients had been systematically monitored and had any infections fully recorded. Since most patients were still alive at the time of the study, several data were confirmed by the patients themselves. According to modern literature findings, IBD patients don't become immunosuppressed by the disease itself, but mainly because of the treatment and the impact it has on their immune system, the response they individually have, and also the environment, findings that until today we cannot quantify [16,17]. Older age is not an important factor for the occurrence of infections, with the exception of TB. In IBD patients there are findings that suggest that bacterial infections, pneumonia, and infections of the urinary tract are more common in older people [18,19].

The frequency of infections in IBD patients was very high in our study, regardless of the type of the disease, its localization and the system affected. Of course, UC patients seem to get infections more often compared to CD patients. At this point, it should be noted that the frequency of infections may be affected by other common comorbidities, like, rheumatoid arthritis, alcoholism, diabetes, chronic pulmonary disease [20].

UC patients were more often affected by microbial infections and by the *Clostridium difficile*, while CD patients were more often affected by viral infections. According to the literature, there are several factors that play a role in the development and deterioration of IBD, and the most common ones are *Mycobacterium avium subspecies paratuberculosis*, *Clostridium difficile*, *Escherichia coli*, *Listeria monocytogenes*, etc. while some parasites may also play a role. It seems that the constant presence of bacterial substances on the gastrointestinal tissue may lead to lower immunity and resistance to bacteria and the development of an infection [21,22].

Clostridium difficile is often found in IBD patients (even more often in UC patients) and has been thought to be the cause of high rates of colectomy and other complications, such as toxic megacolon [23,24]. It is important that 98.2% of the patients had had an infection from the gastrointestinal system. Other affected systems included skin, higher respiratory and the urinary tract. Viral infections mainly affected higher and lower respiratory system, in contrast with microbial infections that affected mainly the gastrointestinal and the urinary system.

In-hospital treatment, which entails a 10-day hospital stay, is an index of the severity of this condition. Patients whose gastrointestinal system had been affected had to stay the longest in the hospital, and CD patients in general had longer hospital stay. According to the literature, it is common that these patients get treated in a hospital, since most of the time they will have to take IV medicines and they should be closely monitored for complications or side-effects [25-27].

In what regards the correlation between infections and type of treatment, it seems that cortisone is linked to higher infection rates, although there wasn't any statistical significance in our study, followed by mesalazine, azathioprine and sulphasalazine; on the other hand the cause of the infection did not have any correlation with type of treatment, excluding patients receiving azathioprine who were more often affected with viral infections. According to the literature, there have been pulmonary infections in IBD patients under treatment with cortisone [28]. It has also been established that IBD patients who receive azathioprine may show problems from the skin or the urinary tract more often compared to those who receive mesalazine [29].

The use of corticosteroids, immunomodulators and anti-TNF factors causes immunosuppression, which in its turn increases the risk of infections that sometimes may have an atypical emergence due to low immunity levels [30,31]. Also, regarding the correlation between infections and type of treatment, methotrexate and infliximab showed higher infection frequency levels, while the majority of the patients affected by an infection (81.2%) did not receive anti-TNF agents. It also seems that patients under treatment with adalimumab are not in high risk of serious infections [32].

Finally, TB affected about 5% of the patients, most of whom received mesalazine and cortisone. It wasn't possible to determine if TB had been properly excluded before the beginning of the treatment, so it is impossible to pinpoint the exact time of the emergence of the infection, thus it is impossible to determine if the infection can be linked to the treatment or it is just a consequence of immunodeficiency, which is in accordance with other studies that have shown high TB rates in IBD patients [33-35].

The present study is an effort to collect and evaluate data of IBD patients gathered in one district over a period of 30 years. The patients trust in our team and the scientists' interest and care are indicative of the study's dynamic. The findings of this study could not be used to make general conclusions about the whole country, although that is something that should be done in the future. It is also important that other data should be evaluated, such as comorbidity, vaccination coverage status, etc. Nevertheless, our sample and the fact that these patients had been systematically monitored over many years, allowed us gather important data that could be linked to other findings from other studies.

Conclusion

The occurrence of infections in IBD patients is quite common, and it could be the product of several factors, such as the patient's age, their treatment, comorbidities and various other factors that alter the final result and make each case different.

Yet the emergence of infections is quite common, and vigilance and alertness are required from the scientific team, so that the infection will be promptly and accurately diagnosed and treated the best possible way. Also, IBD patients should be informed regarding the risk of infections and ways of prevention, and they should immediately seek help from their medical practitioners who know their full history.

Surgical operations on IBD patients, be it ileostomies or any of other kind, could potentially lead to physical disabilities. Those surgeries of course vary according to the disease (CD/UC) and the timing of the diagnosis. But in any case, the patients' situation may be aggravated if they are urgently admitted with terminal ileus.

IBD patients have to deal with several implications that make their daily lives hard. More encompassing inter-scientific approaches and better techniques are needed in order for these patients to be treated by lowering the possibility of disabling implications.

Conflicts of Interest

There is no conflict of interest of any of the authors.

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