Abstract
Ramadan represents the fourth of the five pillars of the Islamic creed. Although patients are exempted from observing this duty, they may be eager to share this moment of the year with their peers. However, there are no guidelines that can help physicians to address the concerns of patients with infectious diseases fasting during Ramadan. For this purpose, we performed a systematic review of 51 articles. Our main findings are that: 1) patients suffering from diabetes at risk of developing infectious complications should not fast; 2) Ramadan fasting has little impact on diarrheal patients; 3) HIV represents a challenge, and ad hoc drug combinations should be recommended to patients, and the patients should be advised not to take fatty meals that could interfere with the treatment; 4) Ramadan has no effect on the effectiveness of anti-helminthic therapy; and 5) patients with active ulcers should not fast, as they have a higher probability of developing complications.

Key words: diabetes mellitus; diarrhea and ulcer disease; HIV; hookworm and tropical infections; infectious diseases; Ramadan fasting.
exist, so we therefore conducted a systematic review that could be helpful to general practitioners.

**Methodology**

The following databases were used: Institute for Scientific Information (ISI) Web of Science (WoS), Scopus, MEDLINE/PubMed, Google Scholar, Directory of Open Access Journals (DOAJ), EbscoHOST, Scirus, and ProQuest. Proper strings made up of a combination of key words such as Islam, Ramadan, fasting, and infection, connected with Boolean operators and using medical subject heading (MeSH) terms, were used where appropriate.

Review articles relevant to the aim of this systematic review were scanned in order to improve the chances of finding potentially relevant studies, and each reference of the potentially relevant articles was manually consulted and screened in an iterative way, until no new references were found.


No time and language filters were applied.

Articles that had direct clinical implications were considered relevant; articles focusing exclusively on Ramadan-induced body modifications assessed with molecular biology and in vitro models were excluded. Studies performed during the month of Ramadan but in which infectious diseases were caused by mass gatherings, such as during pilgrimages, were excluded. Only manuscripts in which infectious disorders were strictly related to the changes of habits and lifestyles during the month of Ramadan were retained.

**Results**

A total of 51 studies (Table 1, divided according to their main topic) were identified and coded. Three studies focused on HIV, three on appendicitis, two on hepatitis, while 31 other research articles described the complications of ulcer disease during Ramadan. Five studies assessed the infectious complications of patients suffering from type 1 and 2 diabetes mellitus. Two studies investigated the infectious complications in urological patients, one study described the impact of Ramadan fasting on diarrheal patients, one investigated the effect of fasting on anti-helminthic therapy, and one study investigated the usage of antibiotics during fasting. One study explored the impact of fasting on tear films and protein composition, and one study reported an anecdotal episode of fulminant meningitis that occurred during Ramadan.

**Usage of antibiotics**

Mikhael and Jasim [2] designed an observational study during the middle 10 days of Ramadan 2014 in two pharmacies in Baghdad, critically assessing 34 prescriptions for adults who suffered from infections. More than two-thirds of participating patients fasted during Ramadan. Usually, most physicians prescribed a mono-therapy with a twice-daily regimen, not taking into account the fasting status of their patient. Doctors should be trained to prescribe long-acting medication in order to prevent treatment failure and avoid provoking bacterial resistance.

**Hepatitis**

Hepatitis imposes a heavy burden, both in terms of clinical management and epidemiology in the Arab world, especially Egypt [3]. Chronic hepatitis patients showed non-significant changes in liver function tests. However, patients with advanced liver disease may decompensate [4,5].

**Diabetes mellitus**

Kobeissy et al. [6] and Schweizer et al. [7] reviewed clinical recommendations for subjects suffering from type 1 diabetes mellitus and advised against fasting for those at risk of infections. This suggestion is valid also for type 2 diabetes, the infectious complications of which were studied by Elmehdawi et al. [8]. The authors conducted a descriptive, retrospective, database-based analysis for the period 2007–2008. They found that infection was the commonest precipitating factor for diabetic ketoacidosis (DKA) during Ramadan (46.6%), followed by lack of adherence and compliance to treatment, even though there was no increase in the incidence and mortality rate for DKA.
## Table 1. Studies divided according to their main topic

<table>
<thead>
<tr>
<th>Investigated topic</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Antibiotics usage</td>
<td>Mikhael and Jasim, 2014 [2]</td>
</tr>
</tbody>
</table>
| Appendicitis                               | Davoodabadi and Akbari, 2005 [49]  
                                        | Davoudabadi et al., 2003 [48]  
                                        | Sula et al., 2010 [47] |
| Diabetes                                    | Al Sifri et al., 2011 [10]  
                                        | Elmehdawi et al., 2009 [8]  
                                        | Kobeissy et al., 2008 [6]  
                                        | Schweizer et al., 2014 [7]  
                                        | Surahio et al., 2009 [9] |
| Diarrhea                                    | Leung et al., 2014 [11] |
| Eye infections                              | Sariri et al., 2010 [52] |
| Hepatitis                                   | Abbas, 2015 [4]  
                                        | Elnadry et al., 2011 [5] |
| HIV                                         | Güven, 2004 [12]  
                                        | Habib et al., 2009 [13]  
                                        | Yakasai et al., 2011 [14] |
| Hookworm and tropical infections            | Sacko et al., 1999 [15] |
| Meningitis                                  | Berthier et al., 1996 [53] |
| Ulcer disease                               | Al-Kaabi et al., 2004 [43]  
                                        | Altaee and Alohaidi, 2011 [42]  
                                        | Athar, 1996 [23]  
                                        | Bdioui et al., 2012a [16]  
                                        | Bdioui et al., 2012b [27]  
                                        | Bener et al., 2006 [40]  
                                        | Chong, 2009 [31]  
                                        | Dönnerici et al., 1994 [24]  
                                        | El Mekkaoui et al., 2013 [28]  
                                        | Elnagib et al., 2008 [39]  
                                        | Emami and Rahimi, 2006 [41]  
                                        | Gali et al., 2011 [46]  
                                        | Goçmen et al., 2004 [37]  
                                        | Gökakin et al., 2012a [25]  
                                        | Gökakin et al., 2012b [26]  
                                        | Golash, 2008 [38]  
                                        | Hossein-Asl et al., 2002 [30]  
                                        | Jastaniah et al., 1997 [22]  
                                        | Kahramanca et al., 2013 [44]  
                                        | Kucuk et al., 2005 [21]  
                                        | Lahbabi, 1957 [20]  
                                        | Leça and Fortesa, 1954 [18]  
                                        | Malik et al., 1996 [35]  
                                        | Mallk et al., 1995 [36]  
                                        | Mehdi and Ajmi, 1997 [34]  
                                        | Mehranbian et al., 2007 [32]  
                                        | Ozkan et al., 2009 [28]  
                                        | Sadeghouri et al., 2012 [17]  
                                        | Shastri-Hurst et al., 2014 [45]  
                                        | Torab et al., 2009 [33]  
                                        | Vach, 1966 [19] |
| Urinary infections                          | Bragazzi, 2014 [50]  
                                        | Salahuddin, 2015 [51] |
Surahio et al. [9] investigated another complication, necrotizing fasciitis. They implemented a prospective observational study that included 35 patients, and found that the major co-morbid factors were old age, diabetes mellitus, hypertension, and renal failure.

Al Sifri et al. [10] investigated the safety of sitagliptin compared with sulphonylureas, in a multicenter, randomized, open-label, pragmatic trial that was reviewed by Schweizer [7]. They recruited 1,066 patients with diabetes mellitus, previously treated with sulphonylureas with or without metformin supplementation. Of the subjects, 529 switched to sitagliptin, while 537 pursued the usual treatment. In the sulphonylureas branch of the study, few adverse effects, including acute pancreatitis and urinary tract infection, occurred.

**Diarrheal disease**

The impact of religious fasting on diarrheal disease has been rarely studied. Leung et al. [11] conducted a retrospective database-based study and used data from the surveillance system of the International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka Hospital, from 1996 to 2012, to compare the pathogenesis and clinical presentation of patients suffering from diarrhea during Ramadan to that of control periods (i.e., 30 days immediately before Ramadan). They found that the prevalence of enteric pathogens was comparable, even though *Shigella* spp. were detected less frequently during Ramadan. The authors speculated that this may be due to differences in food preparation (which is done closer to scheduled mealtime, and served at a higher temperature) and hygiene (increased frequency of hand and foot washing, because of the intense period of prayers). Symptoms during Ramadan among adult Muslim patients were similar to those of patients admitted during control periods, even though patients during Ramadan were characterized by a more severe sense of thirst and a longer hospital stay. There were no differences in the prevalence of severe dehydration, duration of diarrhea, intravenous fluid use, severe complications such as hypotensive shock, or death rate. Slight differences were noticed in patients suffering from cholera. The authors concluded that Ramadan has a scarce impact on the clinical presentation of diarrheal patients.

**HIV**

Sub-Saharan countries such as Ethiopia, Kenya, Nigeria, Somalia, South Africa, Tanzania, and Uganda are plagued by a heavy burden of HIV infection. According to Güven [12], HIV patients may suffer from decreased bone density because of lowered calcium uptake during Ramadan fasting and because of impaired drug functioning. Indeed, some antiretroviral drugs, such as lopinavir, indinavir, nelfinavir, and ritonavir require food consumption, while others such as didanosine, zidovudine, and unboosted indinavir and amprenavir are instead affected by intake of heavy, fatty meals (such as traditional Ramadan meals). Other drugs, such as zalcitabine, delavirdine, indinavir, nelfinavir, and soft-gel saquinavir are affected by dosing schedule, regular frequency of assumption, and concentration. An irregular intake of HIV therapies may impair the clinical outcome, leading to a worsening of the symptoms and favoring the insurgence of drug resistance and to virological failure, as well as altering pharmacodynamics, pharmacokinetics, tolerability, and effectiveness profiles. Moreover, the patients may be exposed to anxiety disorder. On the other hand, fasting could be beneficial, mitigating the adverse effects of HIV treatment, such as hypercholesterolemia and hypertriglyceridemia.

Habib et al. [13] studied treatment adherence and compliance as well as other customary practices such as self-reported health-related quality of life among 243 patients on antiretroviral therapy (ART) (142 willing to fast, 101 not fasting) in Kano, in northern Nigeria, in the period of 23 September to 22 October 2006. Adherence to ART during Ramadan was 96% among fasting subjects and 98% among non-fasting individuals; since commencement of ART, the rates were 80% and 88%, respectively. Observing similar adherence and side effect rates between the two groups and not noticing any impact on body weight and CD4 cell count, the researchers concluded that fasting during Ramadan for HIV patients was safe. Yakasai et al. [14] replicated and confirmed these findings in a sample of 17 heavily treatment-experienced stable patients (10 men) in Nigeria. They compared once-daily to twice-daily dosed ritonavir-boosted lopinavir with fixed-dose tenofovir-emtricitabine once daily. They did not find any changes in treatment adherence and compliance, diarrhea, CD4 cell count, viral load, hematocrit level, kidney and liver function, and lipid concentration. Effectiveness, safety, and tolerability were not affected by Ramadan fasting, particularly changes in nutritional pattern, food behavior, and circadian rhythm. However, two patients (one being fully virologically suppressed) had a post-Ramadan
viral rebound with a significant decrease in CD4 cell count.

Anti-helminthic therapy

Sacko et al. [15] performed a randomized, single-blind, placebo-controlled trial in order to test whether the Ramadan fasting would compromise the efficacy of some anti-helminthic drugs. They tested pyrantel, mebendazole, and albendazole, which are used for the treatment of hookworm infections (*Necator americanus*). The study was conducted in January 1998, in Sikasso, southern Mali, West Africa. A total of 285 subjects were recruited (about 68% of the local population), and hookworm infection was diagnosed in 151 of the subjects. Albendazole proved to be the most effective drug, with an efficacy in the range of 92.1%–99.7%. Fasting did not interfere with the efficacy of the drug.

Ulcer disease

*Helicobacter pylori* causes ulcer disease, whose reactivation and perforation risk is increased during Ramadan [16] because of increased gastric acidity.

This topic has been at least partially covered by the Study on the Epidemiology of Psychological, Alimentary Health and Nutrition (SEPAHAN) systematic review project study conducted in 2012 [17].

An increased rate of ulcer complications during the month of Ramadan had been reported since the early 1950s [18-20], before the availability of anti-ulcer drugs (such as histamine-2 blockers or proton pump inhibitors [PPIs]) and routine endoscopy examination [21].

Jastaniah et al. [22] performed a study that included 27 patients, of whom 25 were males, 2 were females, and the mean age was 36.3 years (range, 21–70 years). Nine patients had a clinical history of peptic ulcer disease with perforated duodenal ulcer over a period of seven years (from 1988 to September 1995). A higher frequency of perforation rates during Ramadan was not observed.

In Qatar, Rashed et al. investigated 2,337 patients admitted during Ramadan and could not find any difference in admissions related to the pathology of the subjects (angina pectoris, hypertension, duodenal ulcer, or bronchial asthma) in Ramadan compared to the previous month [23].

In the United Arab Emirates, Al-Marri et al. studied 150 untreated peptic ulcer patients and found that Ramadan represented a risk factor for ulcer perforation [23].

Dönderici et al. [24] performed a retrospective study from 1987 to 1992. They found that being female and fasting during Ramadan were risk factors for hemorrhage and perforations.

Gökakin et al. [25] performed a retrospective study of 229 patients (195 males, 34 females; 16–85 years, median 45 years; 107 with at least one co-morbidity; only 44 patients regularly taking medication with perforated peptic ulcers from January 1999 to December 2009. A total of 41 patients had undergone operations during Ramadan, with 4.1 operations per month compared with 188 patients with 1.7 operations per month. Fasting during Ramadan was a risk factor for ulcer complications, independent of the duration of fasting, even though the risk was higher in the subgroup that fasted longer (33 subjects fasted more than 12 hours, while 8 fasted for fewer than 12 hours).

This finding was replicated by a subsequent study of the same group conducted from 2009 to 2011 on 321 patients (69 referrals before Ramadan, 132 during the Ramadan, and 120 in the month after the fasting month). The authors found that duodenal ulcers and duodenitis were more frequent during the Ramadan month [26].

Bdioui et al. [27] conducted a retrospective comparative study of 224 cases and found a twofold increase in the frequency of upper gastrointestinal hemorrhage.

El Mekkaoui et al. [28] performed a retrospective study of 291 patients with acute upper gastrointestinal bleeding from 2001 to 2010. Ramadan fast was a risk factor for duodenal ulcer, while it seemed to be a protective factor for variceal bleeding. However, Ramadan had no impact on the clinical outcome in terms of recurrent bleeding frequency and mortality rate.

Ozkan et al. [29] performed a retrospective study comparing patients with acute upper gastrointestinal hemorrhage during Ramadan 2007 to patients with the same complaint during a non-Ramadan month. Having found that a diagnosis of a complicated ulcer was more frequent during the month of Ramadan, the authors concluded that fasting reactivated and aggravated pre-existing gastrointestinal diseases.

Hosseini-Asl et al. [30] designed a cohort study that included 39 patients with duodenal ulcer receiving omeprazole treatment. Ramadan had no influence on the healing rate.

Chong [31] performed a retrospective study from 2004 to 2007 of 1,661 patients with gastrointestinal bleeding episodes due to a variety of causes, from
esophagitis, peptic ulcer disease, and portal hypertension-related pathologies, to neoplasms. A significantly smaller workload was generated during Ramadan, and diagnosis of duodenal ulcer was more frequent during the fasting month.

Mehranbian et al. [32] studied 84 patients with duodenal ulcers who were receiving omeprazole treatment. The healing rate was not different among fasting and non-fasting subjects.

Kucuk et al. [21] performed a retrospective study between 1998 and 2003, comparing 260 patients who underwent operations during the Ramadan, with 10 operations per month, to 210 patients who underwent operations in other months of the year, with 3.8 operations per month (mean age of patients, 40.0 ± 13.0 years; range, 20–85 years; 252 males; 18 patients had at least one co-morbidity; 225 had at least one predisposing factor, including dyspepsia or smoking). They found that fasting during Ramadan may predispose subjects to complications.

Torab et al. [33] performed a retrospective study that included 116 patients (mean age, 35.3 years; range, 20–65 years) with perforated duodenal peptic ulcer from 1 January 2000 to 31 March 2004. With complications occurring in 17.2% of the patients, Ramadan was found to be a risk factor for perforations, increasing them with a relative risk of 5.67.

Mehdi and Ajmi [34] carried out a randomized study with 57 patients (30 fasting and 27 non-fasting subjects) with acute duodenal receiving lansoprazole treatment. Fasting had no influence on the clinical outcomes in terms of healing rate or symptoms.

Malik et al. [35] performed a pilot preliminary study that included a cohort of patients with ulcer disease in treatment with ranitidine; of the patients, 4 had an active duodenal ulcer, 16 a chronic duodenal ulcer, 20 a healed duodenal ulcer, and 1 had a chronic gastric ulcer. Ramadan had no impact on the clinical outcomes. The same researchers [36] performed a subsequent prospective study that included 23 fasting patients (four with an active acute duodenal ulcer, eight with an active chronic duodenal ulcer, eight with a healed duodenal ulcer, two with erosive duodenitis, one with a chronic gastric ulcer) receiving ranitidine treatment. Seven of the eight patients with an active chronic duodenal ulcer and the patient with a chronic gastric ulcer had bleeding episodes during the period of the study. These fasting subjects were compared to 15 non-fasting patients. Endoscopy showed changes in fasting patients, while no changes were detectable in non-fasting patients.

Gocmen [37] studied 1,408 patients admitted to an emergency surgical unit and observed that referrals for perforated peptic ulcer episodes nearly doubled during Ramadan.

Golash [38] carried out a retrospective study from 1996 to 2006 on 152 patients with perforated peptic ulcers who had undergone an open (57 patients) or laparoscopic operation (95 patients). Fasting during Ramadan was a risk factor for complications.

Elnagib et al. [39] conducted a retrospective study from 1999 to 2002 that included 58 patients (52 males, 6 females) with a perforated peptic ulcer. Perforation episodes were more frequent during Ramadan.

Bener et al. [40] designed a retrospective study from 1992 to 2002, recruiting 470 patients with peptic ulcer disease, 215 seen during Ramadan and 255 in the month after Ramadan. Ramadan had no impact on the frequency and outcomes of peptic ulcers.

Emami and Rahimi [41] performed a retrospective study from 2002 to 2004 that included 236 patients with acute upper gastrointestinal bleeding episodes (108 fasting subjects and 128 non-fasting subjects). Ramadan fasting was a risk factor for duodenal ulcers, while it seemed to be protective for esophageal varices. However, Ramadan had no impact on the clinical outcomes.

Altace and Alobaidi [42] conducted a prospective study that included 231 consecutive patients observed from 2007 to 2010 (96 during Ramadan and 135 during the rest of the year; male-to-female ratio of 6:1). They found that fasting during Ramadan was a risk factor for duodenal ulcer perforation.

Al-Kaabi et al. [43] performed a prospective study of 516 patients with ulcer disease (165 observed before Ramadan, 171 during Ramadan, and 180 after Ramadan; 215 males, 301 females) from October 2002 to January 2003. While the frequency of peptic ulcers did not vary among Ramadan and the other periods of the study, duodenal ulcers were more frequent in Ramadan. The proportion of men with ulcer episodes was higher during Ramadan.

Kahramanca et al. [44] retrospectively reviewed 1,460 patients (39.38 ± 13.49 years; 89.4% males; mean fasting period, 13.89 hours) who underwent operations in the years 1962–2012 for ulcer complications. They found that Ramadan increased the risk of complications such as perforation.

Shastri-Hurst et al. [45] performed a retrospective analysis of 209 cases admitted for ulcer disease from 2007 to 2013, but they could not find any relationship between Ramadan fasting and ulcers.
Episodes of peptic ulcers during pregnancy are only anecdotal [46].

**Appendicitis**

Sulu et al. [47] performed a cross-sectional study that included 992 patients with acute appendicitis. Ramadan was not a risk factor for appendicitis.

Davoudabadi et al. [48] performed a cross-sectional study of 1,256 patients with acute appendicitis. They found that significantly fewer patients underwent surgery for acute appendicitis during Ramadan. This finding was replicated by the same group in a subsequent cross-sectional study [49] of 1,773 patients.

**Urinary tract infectious diseases**

In Egypt, Abdel Rahim et al. found that Ramadan fasting seems to protect against urinary tract infections in urological patients [23]. The incidence of urinary infectious diseases in patients with kidney impairment is, indeed, negligible [50,51].

**Eye infectious diseases**

Ramadan fasting seems to modify the protein composition of eye tear film; since it acts as an antimicrobial barrier, its impairment may lead to ocular infections. Sariri et al. [52] investigated the eye film composition in 60 healthy volunteers (35 males and 25 females, 23–27 years of age) before and during Ramadan. They found that the activity of some enzymes such as lysozyme, lactoferrin, and alpha amylase decreased during fasting.

**Other infectious diseases**

Other infection episodes during Ramadan, such as the case of a fulminant meningitis due to *Bacillus anthracis* in an 11-year-old girl [53], are anecdotal.

**Discussion**

The management of patients suffering from infectious diseases or at risk of developing infectious complications is complex and requires a multidisciplinary team. Patients should be carefully checked and assessed, and both the clinical symptoms and laboratory exams should be considered. Also, psychological aspects, such as motivation, and patient preferences and adherence to treatment should be investigated and taken into account. Care through faith- and religion-based practices should be explored [54].

A summary of the key findings of the included articles is presented below. The key findings were that:

1) Patients with uncontrolled diabetes mellitus at risk of developing infections should not fast;
2) Nelfinavir should be taken with meals twice at higher doses instead of thrice daily;
3) Protease inhibitors (PIs) such as lopinavir or ritonavir twice daily or atazanavir once daily should be advised;
4) If possible, PIs can be boosted by Ritonavir;
5) Once-daily dose regimens (combinations such as tenofovir/lamivudine, emtricitabine/efavirenz, or tenofovir/lamivudine/efavirenz) should be recommended;
6) Didanosine usage should be not recommended;
7) Pharmacogenetic tests could be used in order to select those HIV patients who can safely fast and do not have genetic variants related to drug resistance;
8) Patients with prior known ART clinical failure should not fast;
9) HIV patients should be counseled and advised about the meals recommended for breaking the fast (i.e., avoid heavy, fatty meals);
10) Patients with ulcers can safely fast while using a proton pump inhibitor (PPI) if the ulcer is not active and *Helicobacter pylori* has been properly eradicated; and
11) Patients with active ulcers should not fast, since Ramadan fasting seems to be a risk factor for ulcers (particularly duodenal ulcers).

If the patient’s health is stable, the patient’s eagerness to fast should be taken into account and even encouraged, since spirituality plays a key role. Fasting enables the patient to be actively involved in the religious activities and less depressed and isolated [54]. Some studies have shown that religiosity can increase treatment adherence and compliance among HIV patients [12-14].

**Conclusions**

The present systematic review aimed to provide evidence-based suggestions and guidelines for physicians who treat infectious diseases in Muslim patients fasting during Ramadan.

This review showed that patients suffering from any diseases that heighten the risk of developing infectious complications (e.g., active ulcers) should not fast.

However, fasting during Ramadan might not be detrimental for patients suffering from stable HIV,
diabetes, and diarrheal disease. Importantly, physicians should take into account the patient’s eagerness since religiosity (i.e., the degree of commitment to the religion) fosters positive psychosocial outcomes [54] and reinforces treatment adherence and compliance [54] in Muslim patients. As a result, in the case of no medical restriction, fasting should be encouraged in Muslim patients who are enthusiastic about Ramadan fasting. However, these patients should be monitored and instructed to recognize some warning symptoms. Patient empowerment plays a major role in clinical management of diseases.

References

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