Incidence and Economic Burden of Infections in Cancer Patients Receiving Immune Checkpoint Inhibitors: A Retrospective Cohort Study

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Abstract

BACKGROUND

Along with antitumor effects, Immune Checkpoint Inhibitors (ICPI) have shown great potential in treating chronic infections such as HIV, Hepatitis B and malaria, in ex-vivo studies. However, several case reports and case series have suggested an increased infection risk in cancer patients. The purpose of our study was to assess the risk of infections in cancer patients receiving ICPI. We also attempted to evaluate the role of a multidisciplinary approach (Oncology and Infectious disease specialists) and the cost associated with treatment.

METHODS:

Records on all cancer patients over age ≥18 years old who had received at least one dose of ICPI between 2015 to 2018 at a major community teaching hospital in the central Massachusetts region were reviewed. Several risk factors associated with infection were identified. A two-tailed, unpaired t-test was used to analyze the association between risk factors and infection.

We calculated the cumulative length of stay (LOS) and cost per admission with a multidisciplinary vs. non-multidisciplinary approach. The calculated total average cost per admission was compared to a matched population (without an oncologic diagnosis) admitted with infections similar to that in our study, to compare the economic burden.

RESULTS

Retrospective chart review of 169 cancer patients receiving ICPI showed sixty-two episodes of infection in thirty-seven (21.8%) patients and a mortality rate of 3.5% due to associated complications. Risk factors like COPD, prior chemotherapy and steroid use were significantly associated ($P \leq 0.05$) with infections. Further sub-group analysis showed increase in cumulative LOS from 5.9 to 8.1 days but approximately similar average cost per admission ($52,047 vs. $54,510) with non-multidisciplinary vs. multidisciplinary approach. The calculated total cost per admission during an episode of infection in this cohort of patients was $35,484; three-fold higher when matched to similar infections in a general non-oncologic population ($11,527).

CONCLUSIONS

A significant incidence of infections and associated health care resource utilization continues to prevail in cancer patients despite the utility of ICPI. A multidisciplinary approach to manage the infections and associated complications in cancer patients receiving ICPI increased the cumulative LOS but not the average cost per admission.

Background:

Cancer remains the second most common cause of death in the United States, despite a 27% decline in mortality rates from 1991 to 2016.[1] The causes of death in these patients are classified as cancer and non-cancer related, with infection and heart disease being the most common non-cancer related deaths.[2] The risk of infection in these patients is due to a complex interplay between host, environment, and treatment-related factors. The presence of multiple risk factors in the same patient is not uncommon.[3] Several factors predisposing to infection in solid tumors include disruption of natural anatomic barriers such as the skin and mucosal surfaces, obstruction, and treatment-related factors such as chemoradiation therapy, surgery, and the use of implantable devices.[3] Newer therapeutic approaches and antimicrobial prophylaxis continue to shape the spectrum of infections in these patients. While several studies assessed the infection risk with traditional chemotherapeutic agents,[4] the spectrum of infectious complications during and after Immune checkpoint inhibitors (ICPI) is not well established.

Immune checkpoint pathways are inhibitory/stimulatory pathways that regulate the immune system and maintain self-tolerance. Tumor cells express co-stimulatory molecules {programmed death ligand-1, 2 (PDL-1, PDL-2), B28 etc.} that activate the immune check point molecules {programmed death-1 (PD-1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)} on T cells to evade immune-mediated destruction. Several molecules like PD-1, CTLA-4, lymphocyte activation gene-3 [LAG-3], T-cell immunoglobulin and mucin protein-3 [TIM-3] have been identified as immune checkpoint molecules in the recent past.[5] Among them, CTLA-4 is the first clinically targeted immune checkpoint receptor that primarily regulates the early stages of T-cell activation, typically in lymph nodes or spleen. Blockade of CTLA-4 resulted in clonal expansion of cytotoxic T-lymphocytes and therapeutic action against cancer cells. Following the CTLA-4 discovery in 1987, PD-1 was discovered in 1992 by Honjo and colleagues while studying mechanism of T-cell death. PD-1, a member of cluster of differentiation 28 (CD28)/B7 family of co-stimulatory receptors, inhibits T-cell activation by engaging with PDL-1 and PDL-2 in the cancer microenvironment. It is suggested that PD-1 inhibition will have fewer side effects and greater antitumor activity than CTLA-4 inhibition due to its predominant action in the effector phase of T-cell response and increased selectivity for immunosuppressive signals delivered directly by the cancer.[6] Recently, several studies suggested increased response rate with dual blockade i.e. CTLA-4 and PD-1/PDL-1 rather than single agent blockade; although associated with increased toxicity.[7]

Along with augmenting antitumor activity, it is postulated that the ICPIs promote viral clearance in chronic infections by complementing antiviral immune activity. There are reports of a reduction in viral load in an animal model of lymphocytic choriomeningitis infection upon blocking the PD-1 pathway due to restoration of T-cell effector functions.[8] A similar in vivo investigation in humans showed clinical improvement or stabilization of the human polyomavirus, JC virus (JCV) induced progressive multifocal leukoencephalopathy (PML) after receiving pembrolizumab in five out of eight patients.[9] Analysis of the blood and CSF specimens prior to pembrolizumab showed upregulated PD-1, PDL-1 expression on cluster of differentiation four (CD4+) and cluster of differentiation eight (CD8+) lymphocytes, limiting the successful clearance of JCV. Administration of PD-1 blockade (pembrolizumab) prompted down-regulation of PD-1 expression on lymphocytes and an increase in vitro CD4+ and CD8+ anti–JCV

activity.[9] ICPIs continued to show great potential in treating several other chronic bacterial, viral, or parasitic infection, like HIV, Hepatitis B, and malaria by enhancing effector T-cell responses in ex vivo studies;[10] generating a theoretical hypothesis of probable abatement of infections with ICPI in cancer patients. However, several case reports and case series since the initiation of ICPI's use in cancer patients over the past decade reported persistent opportunistic infections risk and reactivation of tuberculosis.[5-8] Review of the literature showed very limited studies assessing the infection risk in cancer patients receiving ICPI.[9,10] Also, given the tremendous overlap of presenting features of ICPI mediated inflammation with infectious processes, these clinical symptoms pose a diagnostic challenge due to the unfamiliarity of the role of ICPI in acute infections. The primary aim of this retrospective study was to assess the risk of infections in cancer patients receiving ICPI. Our study also aimed to assess the economic burden of a multidisciplinary approach to their treatment.

Methods:

A retrospective review of various types of cancer patients receiving PD-1 (pembrolizumab, durvalumab), PDL-1 (nivolumab) and CTLA-4 (ipilimumab) inhibitors between 2015 to 2018 was carried out at a major community teaching hospital (Saint Vincent Hospital Cancer Center) in the central Massachusetts region. All of these patients received immunotherapy, either as an initial agent or later due to initial treatment failure or intolerance. Based on the standard treatment protocols for specific cancer, they were either on single or dual agents.

Inclusion criteria included any cancer patient ≥18 years age who received at least one dose of Immune checkpoint inhibitors.

Exclusion criteria included discontinuation of ICPI prior to initiation due to withdrawal of consent, adverse events from other chemotherapeutic agents, or progression of the disease.

All records of cancer patients receiving Immune checkpoint inhibitors were reviewed. Data extracted included age, gender, body mass index (BMI), cancer type and metastasis sites, comorbidities [congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), diabetes mellitus (DM), chronic infections, autoimmune diseases, and chronic liver disease], medication use such as steroids, granulocyte-colony stimulating factor (G-CSF) and antibiotics, chemo/radiation therapy, ICPI type and number of doses, documented infections or ICPI-mediated inflammation, microbiology data, choice of antibiotics, length of hospital/ Intensive care unit (ICU) stay, mortality rate and the cost per admission with a multidisciplinary vs. non-multidisciplinary approach.

For purposes of the study, various clinically significant events were defined as in Table 1. We also attributed drug-induced pneumonitis or colitis as 'infection mimics' due to their overlapping clinical presentation and/or radiological resemblance.

Table 1. Definitions of Clinically Significant Events.

Type of Infection	Standard Definition
Pneumonia	Clinical symptoms along with supportive radiological findings.
Influenza	Clinical symptoms with positive serologies for influenza type A or B.
Enterocolitis	Clinical symptoms and/or the presence of supportive radiological findings.
Clostridium difficile infection	Identification of C. difficile toxin in stool by enzyme immunoassay in the setting of diarrhea.[18]
Genitourinary infections	Clinical symptoms (flank or suprapubic pain, dysuria, cloudy/foul-smelling urine, increased urinary frequency, or urgency) in the context of a positive urine culture.
Skin, soft tissue, and bone infections	Clinical symptoms (swelling, redness, warmth, pain of skin or skin structures) along with positive cultures (in case of an abscess). For osteomyelitis, clinical symptoms in the setting of supportive radiological findings.
Febrile neutropenia	Core temperature ≥38.3°C or ≥38.0°C for ≥1 hour in association with an absolute neutrophil count ≤500/μL or expected to fall below 500/μL.[19]
Bloodstream infection	Any bacterial infection caused by a recognized pathogen that was isolated from ≥1 blood culture in the context of a compatible clinical illness and the result deemed clinically significant by the treating clinician.
Clinically documented infection	Infection diagnosed by the treating physician based on the identification of a clinical focus (e.g. cellulitis, pneumonia, etc.) but without the isolation of an associated pathogen.
Microbiologically documented infection (MDI)	Bacterial, viral, fungal, and parasitic infections supported by microbiological evidence, such as a positive culture, antigen or PCR test results.

Statistical analysis:

The data was thoroughly explored using univariate analyses. A two-tailed, unpaired t-test was used to analyze the statistical significance of differences in continuous data. All reported *p* values are two-tailed and a *p* value ≤ 0.05 was considered significant. Statistical analysis was done using SPSS software v. 21.0 (SPSS Inc., Armonk, NY, USA).

The study protocol was approved by the local institutional review board.

Results:

A total of 169 patients met the inclusion criteria. The baseline characteristics of the study population are described in Table 2. The median age of the patient population was 68 years {Interquartile range (IQR) = 77 – 62}. In addition to the risk factors mentioned in Table 2, several other risk factors such as neutropenia, recent hospitalization, catheter use, impaired gag reflex, and mucositis were also identified.

Our study only included subjects with solid organ malignancies. Lung cancers constituted more than 50% of the study population. Pembrolizumab and nivolumab were the most commonly used ICPIs. The average number of doses per patient for each of the ICPIs were seven, eight, three and five respectively for pembrolizumab, nivolumab, durvalumab, nivolumab-ipilimumab .

Table 2
The baseline characteristics of our study population.

	Patients with infections (N = 37) 21.8%	Patients without infections (N = 132) 78%	Total (N = 169)	P value
Age (years)	68 ± 1.8	69 ± 1.8	69 ± 1.8	0.42
Gender				
Male	20 (54%)	86 (65%)	106 (63%)	0.1
Female	17 (46%)	46 (35%)	63 (37%)	0.2
BMI	25.7	25.9	25.9	0.8
Risk factors				
Prior chemotherapy	20 (54%)	46 (34.8%)	66 (39%)	0.03
Nicotine use	19 (51.3%)	60 (45.4%)	79 (46.7%)	0.5
COPD	18 (48.6%)	36 (27.3%)	54 (31.9%)	0.01
Steroid use	18 (48.6%)	32 (24.2%)	50 (29.5%)	0.003
Radiation therapy	14 (37.8%)	53 (40.2%)	67 (39.6%)	0.8
Combination chemotherapy	7 (18.9%)	15 (11.4%)	22 (13%)	
DM	6 (16.2%)	22 (16.6%)	28 (16.5%)	
CHF	6 (16.2%)	18 (13.6%)	27 (15.9%)	
Alcohol use	5 (13.5%)	16 (12%)	21 (12.4%)	
CKD	3 (8%)	13 (9.8%)	16 (9.4%)	
Autoimmune	3 (8%)	7 (5.3%)	10 (5.9%)	
Cancers				
Lung cancer	19 (51.3%)	81 (61.4%)	100 (59.2%)	0.2

	Patients with infections (N = 37) 21.8%	Patients without infections (N = 132) 78%	Total (N = 169)	P value
Genitourinary cancer	4 (10.8%)	14 (10.6%)	18 (4.7%)	
Head and neck	4 (10.8%)	9 (6.8%)	13 (7.6%)	
Melanoma	4 (10.8%)	18 (13.6%)	22 (13%)	
GI carcinoma	4 (10.8%)	6 (4.5%)	10 (5.9%)	
ICPI				
Pembrolizumab	21 (56.7%)	70 (53%)	91 (53.8%)	0.6
Nivolumab	14 (37.8%)	41 (31.1%)	55 (32.5%)	0.4
Nivolumab-Ipilimumab	1 (2.7%)	6 (4.5%)	7 (4.1%)	
Durvalumab	1 (2.7%)	5 (3.7%)	6 (3.5%)	

Thirty seven (21.8%) patients developed 62 episodes of infection, and 15 episodes of infection mimics. Microbiology confirmation was available for 13 (21%) episodes and it included bacterial, fungal and viral organisms. The event rates of various infections and the identified microbiology are listed in Table 3. A coexisting diagnosis of drug-induced pneumonitis and colitis existed in 8.2% and 1.7% of cases respectively.

Table 3
Event rates and microbiology of infections after receiving ICPI.

Type of infection	*No of episodes (%)*
Clinically documented infection	**49 (79)**
Pneumonia	31 (50)
Gastroenteritis	8 (13)
Cellulitis	3 (4.8)
Acute cystitis	2 (3.2)
Herpes labialis	1 (1.6)
Osteomyelitis	1 (1.6)
Febrile Neutropenia	3 (4.8)
Microbiologically documented infection	**13 (21)**
MRSA Pneumonia	1 (1.6)
MSSA Pneumonia	1 (1.6)
Stenotrophomonas Maltophilia pneumonia	1 (1.6)
Mycoplasma pneumonia	1 (1.6)
Influenza Type A	1 (1.6)
CMV colitis	1 (1.6)
Clostridium difficile colitis	1 (1.6)
Candida albicans BSI	1 (1.6)
Bacteroides thetaiotaomicron BSI	1 (1.6)
E Coli UTI	1 (1.6)
VRE UTI	1 (1.6)
Pseudomonas UTI	1 (1.6)
Cutaneous abscess due to Bacteroides fragilis, Enterococcus faecalis (Type D), Enterobacter cloacae	1 (1.6)

When comparing the infections and the non-infections group, univariate analysis of risk factors suggested a significant association of COPD (27.3% vs. 48.6%, 95% C.I 0.04 to 0.3, OR 0.375), prior chemotherapy (34.8% vs. 54%, 95% C.I 0.01 to 0.3, OR 2.19), and steroid use (24.2% vs. 48.6%, 95% C.I 0.07 to 0.4, OR 2.96) with infections ($p \leq 0.05$). In case of prior chemotherapy; the use of cisplatin and paclitaxel was the commonest risk factor in those with bacteremia. A concurrent chemotherapy with

pemetrexed and paclitaxel was most commonly associated with febrile neutropenia. Interestingly, we also noted that new-onset neutropenia after starting ICPI (pembrolizumab and durvalumab) and concurrent chemotherapy (pemetrexed and paclitaxel) in lung cancer patients were associated with febrile neutropenia and no cases of infection were identified in patients with neutropenia existing prior to starting ICPI. A mortality rate of 3.5%, due to infections and associated complications, was noted in our study.

The cumulative LOS varied from 2 to 24 days with an average of 7 days. A multidisciplinary team including oncology and infectious disease specialists were variably involved. Oncology and Infectious diseases were consulted in 78% and 50% of cases respectively. Sub-group analysis to assess the role of multidisciplinary approach in managing infections in this set of patients showed increased average LOS from 5.9 to 8.1 days. Yet, the average cost per admission approximately remained the same (non-multidisciplinary vs. multidisciplinary approach - $52,047 vs. $54,510). The total hospital charges to treat the infections and infection-mimics was estimated to be around 2.2 billion dollars ($2,218,035). Upon comparison with a non-oncologic patient admitted with a similar infection, the average cost per admission varied significantly. While the average cost per admission was $11,527 in a general nononcologic patient, the cost increased to $35,484 in a cancer patient receiving ICPI.

Discussion:

Acute infections continue to represent a significant risk in cancer patients irrespective of the choice of antineoplastic therapy. In our study, infections in patients with solid tumors receiving ICPI demonstrated an incidence of 21.8% and an event rate of 36.1%. The event rates were slightly higher than the incidence rates owing to the recurrence of infections. Del Castillo et al. reported a 2% incidence of infections in melanoma patients receiving ICPI, but, the risk increased to 13.5% with steroid or infliximab use.[9] Similar results were noted by Wang et al. in their study on ICPI induced diarrhea and colitis in patients with advanced malignancies.[10] Compared to Del Castillo et al., our study showed much higher incidence rates, owing to the probable immunosuppression from cancer, chronic medical co-morbidities, prior/concurrent chemoradiation therapy, multiple hospital/clinic visits, immunosuppressant use and infection mimics.

Univariate analysis evaluating the association between various risk factors and infections showed a clinically significant association of COPD, prior chemotherapy and steroid use with infections. These results further supported Del Castillo et al. and Wang et al. findings and also suggested an equivalent role of medical comorbidities in increasing risk of infections along with steroids.[9, 10] We also noted that new-onset neutropenia, after starting an ICPI, was associated with a higher risk of infections than pre-existing neutropenia.

Among the several infections that can affect such patients, bacterial pneumonias are a common complication among patients receiving Hematopoietic stem cell transplantation (HSCT) or chemotherapeutic agents, due to their complex immune dysfunction, lung architectural derangements, repeated encounters with the healthcare system and malnutrition.[11] Despite reports of febrile neutropenia

being associated with approximately 10% of in-hospital mortality,[12] the cause of mortality noted in our study was due to pneumonia-related complications (3.5%). With a co-existing diagnosis of drug-induced pneumonitis in 8.2% of the cases, pneumonia was also the most commonly noted infection in our study (Graph 1). Microbiologically documented pneumonia was 6.4% and *Methicillin-resistant Staphylococcus aureus (MRSA), Methicillin-susceptible Staphylococcal aureus (MSSA), Mycoplasma pneumoniae (M. pneumoniae),* and *Stenotrophomonas maltophilia (S. maltophilia)* were the causative organisms. Pneumonia due to *S. aureus and M. pneumoniae* is noted in healthy adults,[13] but, *S. maltophilia* rarely causes pneumonia in immunocompetent hosts;[14] suggesting the increased prevalence being due to the immunocompromised status in these sets of patients. This was further supported by the identification of atypical pathogens in various other infections (Table 3) like *Cytomegalovirus* (*CMV)* colitis[15] and *bloodstream infections (BSI)* due to *Candida albicans (C. albicans)*[16] *and Bacteroides thetaiotaomicron (B. thetaiotaomicron).*[17] Furthermore, various studies only reported the role of ICPIs in a few chronic infections necessitating T-cell mediated clearance until now. Their role in several other infections modulated through other pathways has not been studied and remains unclear.

In the subset of cancer patients receiving immunotherapy, oncology and infectious disease were consulted in 78% and 50% of cases respectively. These significant results suggest the preference of several physicians to seek a specialist's assistance in directing appropriate care, given the novelty of the agents. We also noted a 3.5% mortality rate during admissions for infections, due to several complications, leading to significant health care cost utilization, approximately 2.2 billion dollars ($2,218,035) as total hospital charges. The economic burden due to the infections in this set of patients is three fold higher ($35,484 vs. $11,527), when compared to the general non-oncologic population. The involvement of a multidisciplinary team to manage the infections and associated complications in cancer patients receiving ICPI showed increase in average LOS from 5.9 to 8.1 days when compared to a non-multidisciplinary approach. However, the average cost per admission approximately remained the same in both (non-multidisciplinary vs. multidisciplinary approach) arms ($52,047 vs. $54,510).

Our study has several limitations such as a small sample size, uneven distribution of cancers and ICPI drug type, and the retrospective nature of the study. However, we believe the study provides insight into infectious complications in cancer patients receiving ICPIs and the associated cost burden, in a community setting.

Conclusions:

Our review of the literature showed several studies assessing the use of ICPI in chronic infections requiring T-cell mediated clearance, but limited studies analyzed the association of ICPI with acute infections in cancer patients. With our study showing an infection incidence of 21.8% and the economic burden of 2.2 billion dollars upon healthcare infrastructure, we suggest future studies to address the pathophysiology of ICPI as a risk factor for acute infections. Also, based on the microbiological findings in our study, a high index of clinical suspicion for typical or atypical pathogens, including bacterial, fungal

or viral; is warranted until further studies assess the role of ICPI in immunomodulation for acute infections in cancer patients. A multidisciplinary approach is advised while providing care in this subset of population, given the significant overlap of symptoms between the infection and infection-mimics i.e. drug-induced inflammation and the prevalence of opportunistic organisms.

Abbreviations:

ICPI - Immune Checkpoint Inhibitors, LOS - Length of stay, PDL - Programmed death ligand, PD-1 - Programmed death-1, CTLA-4 - Cytotoxic T-lymphocyte-associated protein 4, LAG-3 - Lymphocyte activation gene-3, TIM-3 - T-cell immunoglobulin and mucin protein-3, CD28 - Cluster of differentiation 28, JCV - John Cunningham virus, PML - Progressive multifocal leukoencephalopathy, CD4 - Cluster of differentiation four, CD8 - Cluster of differentiation eight, BMI - Body mass index, CHF - Congestive heart failure, COPD - Chronic obstructive pulmonary disease, CKD - Chronic kidney disease, DM - Diabetes mellitus, G-CSF - Granulocyte-colony stimulating factor, ICU - Intensive care unit, IQR - Interquartile range, HSCT - Hematopoietic stem cell transplantation, MRSA - Methicillin-resistant Staphylococcus aureus, MSSA - Methicillin-susceptible Staphylococcal aureus, M. pneumoniae - Mycoplasma pneumoniae, S. maltophilia - Stenotrophomonas maltophilia, BSI - Bloodstream infections, C. albicans - Candida albicans, B. thetaiotaomicron - Bacteroides thetaiotaomicron, CMV - Cytomegalovirus; E. coli - Escherichia coli; VRE - Vancomycin-resistant Enterococcus, CDI - Clinically defined infection; MDI - Microbiologically documented infection; HSCT - Hematopoietic stem cell transplantation; OR- Odds Ratio; C.I- Confidence interval.

Declarations:

Ethics approval and consent to participate

The study was approved by the local institutional review board at Metrowest Medical center, Framingham, Massachusetts, U.S.A. The study number is 2019-118. Consent to participate was not eligible as it is a retrospective chart review.

Consent for publication

Approved for submission and publication by all the named authors.

Availability of data and material

The data used to support the findings of this study are available from the first author upon request.

Competing interests – None.

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Author's contributions:

Study design

GA; Data collection – SSN, AN; Manuscript preparation – SSN, PP, AS, GA.

All authors have read and approved the manuscript.

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Figures

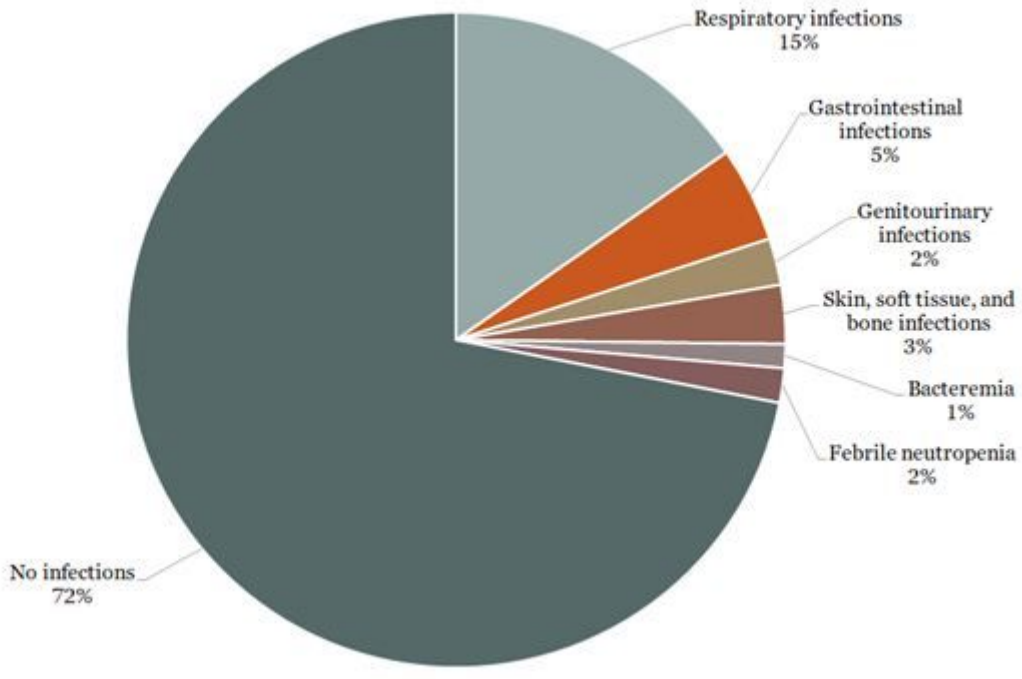

Figure 1

showing Incidence of various types of infections noted in our study.