QATAR UNIVERSITY

COLLEGE OF HEALTH SCIENCE

PREVALENCE OF HEALTHCARE ASSOCIATED INFECTIONS IN ADULTS RECIPIENTS OF AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION IN QATAR

BY

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ABSTRACT

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Title: Prevalence of Healthcare Associated Infections in Adults Recipients of Autologous Hematopoietic Stem Cell Transplantation in Qatar

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Objective

To analyze the prevalence and characteristics of Healthcare Associated Infections (HAI) in patients with hematologic malignancies who underwent Autologous Hematopoietic Stem Cell Transplantation (AHSCT) at the National Center for Cancer Care and Research (NCCCR) newly opened transplant unit in Qatar between October 2015 and October 2016 with global comparison of the bloodstream Infection (BSI) prevalence, one of the most prevalent complications after stem cell transplant.

Methods

The Center of Disease Control (CDC) definitions for laboratory-confirmed bloodstream infection (BSI), modified criteria for pneumonia and hospital-acquired infections were used. Statistical analysis was done using STATA version14. The entire healthcare associated infections (HAI) and other variables were described using means, proportions and 95% confidence intervals. Meta-Analysis of Observational Studies in Epidemiology guidelines was applied in conducting the meta-analysis. The systematic search in English was done in PubMed from 1970 (date of stem cell transplant kick off) to 2016. Inclusion was restricted to human hematology studies that included AHSCT. Statistical calculations allowing an accurate estimation of the prevalence were calculated using MetaXl version 5.3. The data extraction for both studies was done independently by two reviewers.

Results

Out of the sixteen patients, three developed infection leaving the overall infection rate to 18.75%. Chemotherapy induced gastroenteritis was documented in 68.7% of the cases, chemotherapy induced mucositis was documented in 43.7% of the cases. Most of the infections occurred during neutropenia (92.3%) and 69.2% of them during febrile neutropenia.

No gastroenteritis was microbiologically confirmed, all were clinically documented infections. Bacterial infections accounted for 12.5% (2/16 cases) one upper respiratory tract infection and one urinary tract infection. Whereas viral infections, pneumonia and urinary tract infections were each 6.25% (1/16 cases respectively). There was no prevalence of bloodstream infection or central line associated bloodstream infection for any of the patients.

As for the meta-analysis, the aggregated results were studied in the 10 included studies. Significant heterogeneity was noted among the studies (I^2 = 99%; P = 0.0001), the pooled prevalence of blood stream infection among 55789 AHSCT patients from the ten studies was 6%, 95% CI: 0, 33.

Conclusion

This study provides original baseline data about the prevalence of HAI among AHSCT in NCCCR. These findings will be used for additional evaluation of the influence of infection prevention and control measures and therapeutic plans for these patients. They will also contribute to the enhancement of the quality of care in NCCCR, mainly in the hematopoietic stem cell transplant unit (HSCT) through the proper implementation of the infection control standards and proper implementation of antimicrobial stewardship program.

DEDICATION

This thesis work is dedicated to the loving memory of my father and mother.

To my husband, Marwan, who has been a constant source of support and encouragement during the challenges of MPH and life. I am truly thankful for having you in my life.

To my daughters Tia, Chloe and Lynne, you have made me stronger, better and more fulfilled than I could have ever imagined. I love you.

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CHAPTER 1: INTRODUCTION

Types of Healthcare Associated Infections

The HAIs are of two types: 1-The endogenous infections are infections that occur when the patient is contaminated by his own germs. The patient's medical situation, i.e. his age and pathology, his treatment, the quality of care and the presence of pathogenic germs for certain fragile patients, are involved. 2-The exogenous infections that are either infection transmitted from one patient to another, or infections caused by the germs of the carer or linked to the contamination of the hospital environment.

The origin (causes) of these infections are a lack in hygiene practices: it has recently been shown that the major cause of bacterial transmission is lack of hygiene, mainly lack of hand washing (1). Advances in medicine and surgery with, for example, increasingly aggressive care and therapeutics, may be a possible source of infection. For the most part, the main distinguished HAIs are the infections of superficial or deep surgical wounds (Surgical Site Infections or SSI), the urinary tract infections (symptomatic and asymptomatic bacteriuria), the primary bacteremia (Bloodstream Infection or BSI) / sepsis, the respiratory infections (pneumonia) and catheter infections.

The most affected services, in descending order, are intensive care units, surgery, and medicine. Lower risk services are pediatric and psychiatric services and among the bacteria responsible for infections in hospitals, the proportion of multidrug-resistant strains is among the highest globally (2)

Burden of Healthcare Associated Infections

Healthcare associated infections (HAIs) are recognized as major public health problems due to their frequency, cost and severity. The risk of contracting a hospital infection in

the U.S is 1 in 25 patients and this figure varies depending on the service in which the person is hospitalized for. It can reach higher numbers in a service like intensive care unit (3). According to the Center of Disease Control (CDC), HAI Data and Statistics 2011, the types of the most prevalent nosocomial infections are pneumonia, gastrointestinal infections (GI), urinary tract infections (UTI), primary blood stream infections and surgical site infections (SSI)(4).

Moreover, HAIs lead to prolonged hospital stays. This may lead to 10.7 additional days in hospital on average per case of nosocomial infection reaching 16.7% cumulative mortality due to infections a year after infection (5). Some patients suffer long-term impairment and some others lose their lives.

The human cost is unacceptable. Other than the physical effect and death, the adverse event for the patient is a source of stress and affects the morale and leads to added suffering and psychological burden.This was clearly mentioned in one of the CDC reports, higher rates of nosocomial infections contributes to increased mortality rates, and a negative increase in patient outcomes (4). Since HAI is naturally linked to health-care workers' behavior like substandard hand hygiene practices and sometimes to health-care system breaches (e.g. unavailability of the right equipment), this load will definitely lead to an intense disappointment and mistrust in the system and health-care professionals (6).

Each year, the treatment and care to hundreds of millions of patients worldwide is complicated by these infections acquired during health care stay. Some patients are then in a more serious condition than would have been under normal circumstances. The HAIs rates mainly depend on the acuteness of disease, on medical interventions and having invasive devices and undergoing procedures, especially ventilator use, central venous

catheters (CVCs) and urinary catheters use (7). Many of these infections are resistant to at least one antibiotic. Antibiotic resistance generates $ 16.6 billion to $ 26 billion per year in additional costs to the healthcare system of United States (8).

In addition, when speaking about the financial cost, in case of severe sequelae, the infection sometimes leads to disability, loss of income or job loss. Not to forget about the economic and social cost ending up with increased number of procedures, increased antibiotic treatments, increased care prices and as a result the health care systems bears a heavier financial burden (9).

Complications of healthcare associated infections in autologous hematopoietic stem cell transplant recipients

The AHSCT patients are commonly susceptible to infections during the pre and recent post-engraftment phase and this infection risk remains up to six to twelve months after the transplant. The common types of infections after AHSCT are pneumonia, which is one of the frequent complications in the early post-engraftment phase, sometimes with invasive aspergillosis or with the reactivation of the cytomegalovirus (CMV). Diarrhea can occur as well in the early post engraftment phase: it can be of non-infectious origin or infectious such as Clostridium Difficile diarrhea. Bloodstream infections (BSI) are also common in the AHSCT patients. They are mainly related to the central venous access or caused by mucosal barrier injury (gastrointestinal tract or lungs). Hepatitis B seroconversion and development of acute hepatitis especially can occur in patients diagnosed with multiple myeloma. Neutropenia and neutropenic fever are also common complications during the pre-engraftment period. Mucositis, mucosal inflammation, occurring on the digestive tract (oral cavity, oropharynx and esophagus) during

myeloablative conditioning regimens is a common complication and it is principally due to mucosal injury (10).

Significance and implication

The National Center for Cancer Care and research (NCCCR) part of Hamad Medical Corporation was inaugurated in 2004.Hematopoietic stem cell transplantation is a potentially curative therapeutic modality for many hematologic and non-hematologic conditions. As a fruitful outcome of Qatar's National Cancer Strategy, the hematopoietic stem cell transplantation program has been started in the NCCCR in October 2015. Since the opening of this new service, no surveillance studies were conducted to estimate the prevalence of HAIs in the first year of operation. What is currently done is the routine infection prevention and control surveillance and routine reporting of the infections encountered without special segregation for hematopoietic stem cell transplant patients. The study findings will help in monitoring and tracking future HAIs in AHSCT as well as in setting a baseline for future studies in this population.

To our best of knowledge, there were no meta-analysis conducted to quantify the prevalence of one or all of these infections and complications in patients who underwent AHSCT.

Aim

The aim of the study is to contribute to the improvement of the quality of care in Hamad Medical Corporation (HMC) cancer center, mainly in the hematopoietic stem cell transplant unit (HSCT) through the proper implementation of the infection control standards.

Objectives

- To assess the prevalence of HAIs and infectious complications among the AHSCT patients up to discharge and set the baseline for future studies in NCCCR.
- To identify overall and site specific infection rates and mortality among the AHSCT patients up to discharge.
- To estimate the global prevalence of BSI, one of the most prevalent HAIs among the AHSCT and compare that among different populations.

Research questions

- What is the overall and site-specific prevalence of healthcare associated infectious complications in AHSCT at the new NCCCR transplant unit a year after functioning?
- What is the global prevalence of blood stream infection, one of the most common health care associated infectious complications after an AHSCT?
- How is this prevalence in the new NCCCR HSCT unit compared with that in other populations?

CHAPTER 2: LITERATURE REVIEW

Prevalence of healthcare associated infections worldwide

Estimates of the extent of the problem are limited by the lack of reliable data. The consequences on health care facilities and the communities are unknown in most countries.

No health facility or country or health system can claim to have solved this problem with HAI still affecting hundreds of millions of people worldwide and being a major problem for patient safety.

In modern health facilities and developed countries, 5 to 10% of patients acquire one or more HAI. “In developing countries, the risk of HAI is 2 to 20 times higher than in developed countries; the proportion of patients affected can exceed 25%. In intensive care units, the HAI affect approximately 30% of patients, and the associated mortality can reach 44%” (6).

HAI is causing more serious illnesses, extension of the length of hospital stay, long-term impairment, unwanted mortality, additional economic burden and high individual personal costs for clients. It was demonstrated that the validated and standardized prevention strategies can reduce 50% of the HAI. Most preventive measures are simple and inexpensive; they can be implemented both in developed countries and in countries with limited resources (6).

The Study on the Efficacy of Nosocomial Infection Control (SENIC) showed that over 30% of HAI can be avoided with a good infection control program (11). The European

Prevalence of Infection in Intensive Care (EPIC) study on the prevalence of HAI in intensive care units emphasized on the importance of taking the specific measures for infection control and prevention in critically ill patients (12).

Risk factors of healthcare associated infections

Many risk factors contribute to HAI such as the use of invasive equipment or catheters, and certain patient's populations such as trauma, burns or immunocompromised patients who are more susceptible groups (13).

In addition to the usual risk factors for community urinary tract infection, the main risk factor for nosocomial urinary tract infection is the existence of a urethral catheter. The risk of nosocomial urinary infection increases with indwelling catheters.

Artificial ventilation is the main risk factor for respiratory tract infections and pneumonia infection. The intubation probe and the tracheotomy cannula are foreign bodies; they necessarily involve an inflammatory process of the laryngeal and / or tracheal mucosa on contact with them.

Infections of the surgical site are caused by the patient's endogenous skin flora or by breaking the aseptic operative technique, or inappropriate preoperative antibiotics administration, or the operating room environment, or bacterial, viral, and fungal contamination presented by the operative staff (14).

Intravascular devices are the gateway to infections due to the breakdown of the natural skin barrier. The infectious risk increases with the duration of maintenance of the central venous catheter and the frequency of manipulations on the infusion line. Intravascular devices are the major source; accounting for about third of nosocomial blood stream

infections. A remote infectious focus may also be associated with nosocomial bacteremia, particularly a urinary, pulmonary and digestive focus. Prolonged neutropenia is also one of the main risk factors, so permanent attention should be given to the problem of nosocomial infections particularly in high-risk patients. Hospitals should actively participate in the fight against infections and this should be part of a continuous quality improvement (15)(16).

Complications of healthcare associated infections

Septicemia or bloodstream infection caused by central venous catheters represents a major category in HAIs. The mortality and morbidity risk of these infections is high (50%) and the reduction in their prevalence may be achieved by preventing infections. Prevention of sepsis caused by central venous catheters therefore deserves the attention of every health care institution and every health professional (17).

In a national approximation of the death related to HAIs conducted by the Centers for Disease Control and Prevention in the US hospitals in 2002 where they used diverse approaches along with three data sources, among them the National Nosocomial Infections Surveillance (NNIS) system data, the numbers of "estimated death related to HAIs were 98,987. Of these, 35,967 were related to pneumonia, 30,665 to bloodstream infections, and 13,088 to urinary tract infections, 8205 to surgical site infections, and 11062 for infections of other sites". This national approximation deduced that the HAIs in hospitals are a noteworthy source of morbidity and mortality in the United States (9).

But death related to HAI varies according to the place of hospitalization with 30% of the HAIs observed in intensive care units accounting for notable and significant morbidity

and mortality rates (13).

Prevalence of healthcare associated infections in immunosuppressed patients

Any person admitted to a healthcare facility is likely to develop an infection. Those who are particularly sensitive are the ones with immune deficiency. Infectious complications after hematopoietic stem cell transplants are frequent and potentially severe.

In hematology, aplasia will be the consequence of the chemotherapy effect on the bone marrow and the risk of infection will be high. In fact, the white cell count drops to a figure lower than 500 / mm3, with reduction particularly in polymorph nuclear which are the main anti-bacterial and anti-fungal agents.Therefore, the high prevalence of HAI is a recurrent complication in patients with hematological malignancies, due to the harshness of their disease that regularly lead to severe immunosuppression ,due to the chemotherapeutic agents, ending up with central line associated blood stream infection as one of the most frequent types of infections (18).

After AHSCT, patients are at remarkable risk of getting one or more HAIs, especially during the neutropenia phase of their treatment. Infection occurs mainly because of immunosuppression and the most important phase to be considered is the neutropenic status post engraftment. In this particular phase, infection prevention and control measures are essential (19). Bacterial infections are the most dominant and they cause many complications. They mostly cause bloodstream infections, pneumonia and gastrointestinal infections (20).

Among the hematology-oncology patients with neutropenia, the prevalence of central line associated bloodstream infection is the highest and there is a high recommendation for

the infection rates to be monitored in hematology-oncology wards (21).

The effect of bloodstream infection is evident throughout the post-hematopoietic stem cell transplantation (HSCT) period. Bloodstream infection (BSI) is significantly associated with death throughout this post-HSCT period (22). The different risk factors associated with HAI were the prolonged neutropenia days and the duration of fever (23).

Several authors have provided information on these special aspects. Infection is responsible for the majority of deaths after allogenic and autologous transplants. Hospital associated infections such as bloodstream infections, pneumonias and diarrhea are common among these particular patients and account for significant costs and morbidity (24).The infectious risks of HSCT and the measures to decrease these complications were reviewed by Magauran et al. Of these measures, many are related to healthcare worker's behavior and environmental control. Of course, the challenges will remain for clinicians despite the marked advances in the field of HSCT. These measures need to be implemented prior to transplant and during the engraftment phases (24).

The long neutropenic period <1 × 10(9)/L beyond nine days, was found to be the single risk factor for bacteremia. Pinana et al. (22) wrote "the identification of such risk factors may be helpful to implement prophylactic and therapeutic risk-adapted strategies to reduce the prevalence of bacteremia in AHSCT".

The evaluation of the profile of bloodstream infections in patients after HSCT was described in a polish study that was conducted in patients after HSCT in 5 centers of the Polish Pediatric Group for Hematopoietic Stem Cell Transplantation in 2012-2013. The study showed that the description of BSI rely on the latent illness and HSCT donor type

(25).Consideration should also be given to potential viral reactivations in autologous HSCT patients (26).

The intensive use of chemotherapy, development of surgery and radiotherapy techniques and mastery of supportive care has led to significant improvement in the survival of cancer patients. Nevertheless, the aggressiveness of the treatment and the use of increasingly frequent invasive procedures, such as central venous access, expose this vulnerable population to infectious complications. These are a major cause of morbidity and mortality patients with cancer. These infections prolong hospital stay and increase the cost of its management significantly. Therefore, the implementation of strategies to fight against these infections is critical. The neoplastic disease and the aggressiveness of treatment are responsible for a deep and prolonged immunosuppression, which increases the risk of infection in oncology- hematology patients. When monitoring these infections, the factors of intrinsic and extrinsic risk can be analyzed, microbial and evolution of bacterial resistance to antibiotics can be studied, progress and identify areas of prevention can be monitored (27).

Surveillance of healthcare associated infections

This worldwide burden of the HAI stays obscure due to the difficulty assembling solid and reliable information. In hospitals, ambulatory and long-term care, HAI gives off an impression of being a hidden, crosscutting issues that no organization or nation can claim to have illuminated yet. HAI surveillance is needed, it is complicated and necessitates the utilization of systematic standards, handiness of diagnostic facilities and competence to conduct it and interpret the results. Surveillance frameworks for HAIs do exist in a few

high-income nations and yet are nonexistent in most low-and mid-income nations (6).

In the 1970s, U.S public health officials paid heed to expanding numbers of HAIs and their consequences of expanded hospital costs, morbidity, and mortality. Healthcare facilities started applying infection control programs; in any case, their effectiveness was un-evidenced. In 1974, Haley and others at the CDC (28) composed the SENIC national Project to look at whether disease control and surveillance projects could bring down the rates of HAIs. This study performed over a 10-year time span (1975 to 1985), inspected HAI rates in a sample of United States clinics before and after applying the infection control programs. This project demonstrated that the rates of the four common HAIs were "reduced by 32% by applying programs comprising surveillance with feedback of infection control rates to hospital staff, enforcement of preventative practices, supervision by infection preventionist to collect and analyze surveillance data, and the involvement of a physician or microbiologist with specialized training in infection prevention and control" (28).

This study has affirmed the success of infection control surveillance programs and empowered an expansion in their quantities all through healthcare facilities in the United States. In the early 1990s, following the experience of the National Nosocomial Infections Surveillance System (NNIS) in the United States, several European countries began to set up surveillance network. In 1994, a first coordination was financed by the European Commission, as part of the creation of the Hospitals in Europe Link for Infection Control through Surveillance (HELICS) program. In 1998, a mandate to standardize the epidemiological surveillance of communicable diseases was given to the

HELICS network. The Institute of Medicine published in 2000 “To Err Is Human*:* Building a Safer Health System*”* and subsequently drew attention to preventable medical errors, including HAIs and patient safety (29).Then in 2003, the Joint Commission issued the first-ever National Patient Safety Goals requiring from each accredited hospital to show their programs that inscribe the reduction in healthcare associated infections as a target vis-a-vis enhancement of the patient safety. They particularly endorsed the conformity to the CDC or the World Health Organization’s hand hygiene guidelines and the reporting of death related to Healthcare associated infections as an “unanticipated event not related to the natural course of the patient's illness” (30).

The Surgical Site Infection Network was created in Denmark and the septicemia network in Belgium is among the first set up. In 2002 and 2003, the HELICS network produced standardized protocols for SSI surveillance and nosocomial infections in resuscitation. From 2005 to 2008, surveillance continued under the Improving Patient Safety in Europe (IPSE) network (31).

Infection surveillance and control programs began expanding after the report of SENIC was out. They started using a standardized surveillance methodology, the infection rates were reported through databases such as the National Nosocomial Infection Surveillance system that was replaced in 2005 by the National Health Safety Network (NHSN) based at the CDC. Elements of this novel system started to be followed worldwide.

The Council's recommendation of 9 June 2009 encouraged the European Union member states to organize periodic prevalence surveys. It confirmed the importance of targeted surveillance for certain types of infections, such as SSI. It also underlined the essential

role of an early warning system and it recommends using the indicators of organization or means proposed by the European CDC.

Prevalence surveys on SSI have also been the subject of a European protocol in 2010. The purpose of these surveys was to sensitize hospitals to the surveillance and prevention of healthcare acquired infections, to assess their importance and to describe them, and to evaluate national strategies when these surveys are repeated.

Many developed countries in Europe and Americas are now having proper hospital surveillance for infections and they are giving a big attention to infection prevention and control programs that can reduce the rates and sometimes eliminate the HAIs.

In Qatar, the HMC Infection Control program was established in the late eighties and has expanded enormously throughout the years to comprise in 2016 a team of 25 persons distributed across its eight facilities. The aim of the Infection Prevention and Control program (IPAC) in HMC is to protect patients, protect healthcare personnel, and promote safety, quality, and value in the healthcare delivery system. The program is comprehensively maintained, outlining the structure and function throughout the organization. The Infection Control Corporate Committee and the Infection Control Team from each HMC facility have the responsibility for monitoring it.

The multidisciplinary, systematic and coordinated approach was developed to minimize the risk of spread of infections between patients, family, health care workers and visitors.

The IPAC within HMC facilities has a well-defined written plan and takes into account the goals, mission statement, and the annual review of surveillance data and risk

assessments of each facility's infection control program. The surveillance system for health care associated infection is prioritized based on the high risk and high volume of procedures and treatment, which includes device-associated infections such as central line associated bloodstream infection, ventilator associated event and catheter associated urinary tract infection, procedure associated infection such as SSI including implant surgeries and multi-drug resistant organisms. The documents, reports of data analysis and recommendations are provided to leadership on a quarterly basis (32).

CHAPTER 3: METHODS

Two studies were conducted. The first is the NCCCR study to assess the prevalence of HAIs, the infectious complications and site specific and overall infection rates and mortality among the AHSCT in Qatar. The second is the meta-analysis conducted to estimate the global prevalence of BSI, one of the most prevalent HAIs among the AHSCT and compare that among different populations including Qatar.

NCCCR Study

Descriptive NCCCR study assessing the prevalence of specific hospital associated infectious complications post AHSCT and the mortality related. Data was collected from the electronic medical records of all AHSCT patients who attended the HSCT unit in the NCCCR from October 2015 to October 2016.

Study population

The inclusion criteria for the cases were adult patients of 14 years and above, who underwent AHSCT in NCCCR between October 2015 and October 2016. Sixteen autologous-transplanted patients were identified.

Ethical consideration

The study relied on data extraction from electronic medical records and it did not require informed consent from the study participants as no contact was made with anyone of them. HMC and Qatar University IRB committees gave the ethical approval. For both studies, data collection and entry were validated by two qualified practitioners along with the researcher for quality assurance purposes and stored confidentially in her office on

locked access computers.

Data collection

Data collection from the electronic record of each patient and the hospital stay from admission to discharge were reviewed up to discharge. Complications related to hospital infection were compiled. From the electronic medical records, confirmed infections by microbiology laboratory for tests that were previously obtained mainly from blood and urine culture results, stool samples and soft tissue swabs where compiled as well. The isolates that were confirmed by the microbiology laboratory were assembled into bacterial families. The presence of localized infections, with or without microbiologic confirmation was used to determine clinically documented infections or microbiologically documented infections. Patients who suffered from diarrhea, Clostridium Difficile infections were accounted for toxin-producing strains and diarrhea without positive stool culture or clinical manifestation of infection was recorded as chemotherapy induced diarrhea. All the positive microbiological tests without clinical manifestations, like skin-commensals, were not considered. The isolation site was used to determine the type of infection and was divided into bloodstream infections (BSI) and central line associated bloodstream infections, urinary tract infections (UTI) and catheter associated urinary tract infections, gastroenteritis, mucositis, bacterial, fungal or viral infection, and pneumonia. All significant pathogens from blood cultures and physician's notes for oral mucositis and diarrhea were considered. The prevalence of infection was obtained based on the CDC definition of HAI. If the patient had the same infection twice, within a window period of 14 days, it will be considered as same infection.

The variables extracted were: age, sex, diagnosis, comorbidity, febrile neutropenia, mean duration of neutropenia, infections during neutropenia, antibiotic administration and death all during the 30 hospital days.

Data collection tools

The tools that were used to collect the data:

1) Electronic medical records system in NCCCR.
2) Developed data collection sheet (appendix B), based on NHSN and CDC latest criteria (January 2017).

Main outcome variables

1) Specific Hospital Associated Infectious complications post AHSCT
   - Pneumonia
   - Bloodstream infection (BSI)
   - Central line associated blood stream infection (CLABSI)
   - Urinary tract infection (UTI)
   - Catheter associated urinary tract infection (CAUTI)
   - Gastrointestinal infection
   - Mucositis
2) Mortality related to these Hospital Associated Infectious complications post AHSCT.

Statistical analysis

The basic statistical descriptive methods were performed using STATA software version14. The entire healthcare associated infections (HAI) and other variables were described using means, proportions and 95% confidence intervals.

Meta-analysis

Search methodology

For the meta-analysis, the synthesis that took place followed a rigorous methodology ensuring the impartiality of the synthesis and its reproducibility. The systematic review was conducted in conformity to the Meta-Analysis of Observational Studies in Epidemiology guidelines. I ran a systematic search in English in PubMed from 1970 (date of stem cell transplant kick off) to 2016 using search terms as MeSH “Stem cell" OR "marrow" OR “cord”, OR “autologous “AND "transplant" AND “BSI” OR “bloodstream infection” OR “sepsis” OR “bacteremia “OR “clabsi” OR “complications” AND “humans”.

Inclusion criteria

Inclusion was restricted to human hematology studies that included autologous hematopoietic stem cell transplant, full-text articles written in English and studies reporting infections/complications after AHSCT. Studies performed on pediatric population and studies that presented data in a non-extractable format (i.e., infection in two types of transplants together) were excluded.

Data extraction

For the data extraction, two reviewers (J.D.N and M.A.H.S) separately appraised all abstracts for studies that met the eligibility criteria as well as citations by titles. Articles with full-text version of all potentially relevant studies were retrieved and separately assessed for illegibility. Relevant information from the text, tables, and figures of eligible articles were gathered and summarized using an excel spreadsheet. Unanimity was attained if there were any dissimilarity among the reviewers.

The following data were obtained: the characteristics of each study, including the study design, the country of origin, and the study period. I also obtained information on the patient population including prevalence of BSI in the AHSCT patients' population.

Quality assessment

I used the modified Newcastle-Ottawa Quality Assessment Scale for case-control as well as for cohort studies to evaluate the quality of the studies (appendices C and D). The scales assessed whether the authors tackled the measures against bias. The quality criteria were combined into a score composed of one variate, as shown in table 5 and table 6. The Quality score was established on a new scale between zero and one (Qi score); it was done by adding the points of each component and dividing it by the highest sum obtained by a study within the meta-analysis, the best quality study will have a Qi of one. In the Cohort studies, the cohort representativeness had 2 points if it was truly representative and 1 point if somewhat representative. The case selection for non-BSI had 1 point if it was drawn from the same community as the BSI cases, zero point if drawn from another source. Ascertainment of exposure got 2 points if it was taken from a secure record and 1

point if it was from interview or self-written report. The demonstration of the BSI not present at start had 1 point if it was not present and zero if it was present at the start of the study. The assessment of the outcome received 2 points if it was independent/blind, 1 point if it was taken from a record and zero points if self-reported or no information. The comparability got 1 point if the study adjusted for confounders and zero points if not. In the Case control studies, the case definitions had 2 points if the validation was independent, 1 point if from records or self-report and zero if no information. The case representativeness had 1 point if it was representative and zero if potential selection bias. The selection of controls got 2 points if it was taken from the community and 1 point if it was from the hospital. The definition of controls had 1 point if BSI was not present at the start and zero if no information. The ascertainment of exposure received 2 points if it was taken from secure records, 1 point if it was self-reported or no information. The comparability got 1 point if the study adjusted for confounders and zero points if not.

Statistical analysis

The primary outcome of interest was the prevalence of BSI among AHSCT patients. It was pooled using IVhet and QEM (33) (34) and displayed by forest plot.

Statistical calculations allowing an accurate estimation of the prevalence were calculated using MetaXl version 5. Heterogeneity was assessed with Tau–squared statistics. A subgroup analysis was done by geographic location (USA versus Europe and India) to check if there was a difference in BSI rates and per antibiotic prophylaxis to check whether antibiotics had an effect on reducing BSI rate. The funnel and Doi plots were examined to assess the possibility of publication bias.

CHAPTER 4: RESULTS

Descriptive National Center for Cancer Care and Research (NCCCR) study

Characteristics of the patients are presented in Table 1. In the analyzed period of time, from October 2015 to October 2016, 16 patients underwent AHSCT. The mean age was 46.37 (range 31 to 57years), SD 8.30 and majority were males 11(69%).

Eleven (69%) patients were diagnosed with multiple myeloma, 1(6%) with a refractory plasmacytoma, 1(6%) with relapsing diffuse large B-cell lymphoma (DLBCL), 2(13%) with refractory Hodgkin lymphoma and 1(6%) with relapsing Mantle cell lymphoma. The mean duration of neutropenia was 6.31 days (range 4 to 10 days). Comorbidities as well as febrile neutropenia were present in 9 patients (56%). There were 12(75%) patients who had infection during neutropenia and during the 30 hospital days, 14(87.5%) patients received antibiotics and no death was observed in any of the patients up to discharge.

Table 1 Characteristics of AHSCT recipients

	Frequency (%)
Number of patients	16(100)
Mean age –Years	46.37
Sex	
Male	11(69)
Female	5(31)
Diagnosis	
Multiple myeloma	11(69)
Refractory plasmacytoma	1(6)
DLBCL	1(6)
Refractory Hodgkin lymphoma	2(13)
Mantle cell lymphoma	1(6)
Comorbidity*	9(56)
Febrile neutropenia	9(56)
Mean duration of neutropenia- days	6.31
Infection during neutropenia	12(75)
Infection during hospital stay	12(75)
Antibiotics	14(87.5)
Death	0(0)

*Comorbidity includes diabetes, hypertension, renal impairment and rheumatic heart disease

The Prevalence and characteristic of infection are presented in Table 2. Infectious complications during neutropenia accounted for 92.3% of the patients. Among patients with infections, febrile neutropenia accounted for 69.2% (9/16 cases).

Clinically documented infections were more prevalent (11/16 cases) than the microbiology documented ones (2/16 cases).

Table 2 Characteristics of AHSCT recipients with infectious complications according to diagnosis and neutropenia status

	With infection N (%)	*MDI N (%)	*CDI N (%)
Diagnosis			
Multiple myeloma	8(61.5)	0(0)	8(72.7)
Refractory plasmacytoma	1(7.6)	1(50)	0(0)
DLBCL	1(7.6)	0(0)	1(9.1)
Refractory	1(7.6)	1(50)	0(0)
Mantle cell lymphoma	2(15.3)	0(0)	2(18.2)
Febrile neutropenia			
Yes	9(69.2)	1(50)	8(72.7)
No	4(30.7)	1(50)	3(27.7)
Infection during neutropenia			
Yes	12(92.3)	2(100)	10(91)
No	1(7.7)	0(0)	1(9)

*MDI: Microbiologically documented infection CDI: Clinically documented infection

The infectious complications encountered in the AHSCT recipients are presented in table 3a. Out of the sixteen patients, three developed infection leaving the overall infection rate to 18.75%. Most of the infections occurred during neutropenia (92.3%) and 69.2% of them during febrile neutropenia. There was no gastroenteritis microbiologically confirmed, all were clinically documented infections. Bacterial infections accounted for 12.5% (2/16 cases) one upper respiratory tract infection and one urinary tract infection. Whereas viral infections (Cytomegalovirus), pneumonia and urinary tract infections accounted each for 6.25% (1/16 cases respectively) of the infections. There was no prevalence of bloodstream infection or central line associated bloodstream infection for any for the patients. As for the chemotherapy induced complications, gastroenteritis and

mucositis had, with respectively 68.7% and 43.75% as shown in table 3b.

Table 3a Infectious complications encountered in the AHSCT recipients

	No*	Percentage	95% CI
Overall infection	3	18.75	5.3%-48%
Bacterial Infection	2	12.5	3.5%-36%
Fungal infection	0	0	0%-19.3%
Viral Infection	1	6.25	1.1%-28%
Pneumonia	1	6.25	1.1%-28%
Bloodstream infection (BSI)	0	0	0%-19.3%
Central line associated blood stream infection	0	0	0%-19.3%
Urinary tract infection	1	6.25	1.1%-28%
Catheter associated urinary tract infection	0	0	0%-19.3%

Table 3b Chemotherapy induced complications in the AHSCT recipients

	No*	Percentage	95% CI
Gastroenteritis	11	68.7	44.4%-85.8%
Mucositis	7	43.75	23.1%-66.8%

Meta-analysis

Yield of search strategy

The search strategy determined 2588 unique publications, the titles of which were screened one by one for inclusion, 2444 were excluded due to outcomes other than BSI (irrelevant articles, one prevalence of all types of infections, not only BSI and articles with pediatric population). Neither meta-analysis (13, all irrelevant) nor systematic

reviews relevant to the search criteria (48, all irrelevant) were found. The abstracts of the remaining 144 studies were screened for inclusion of which 108 studies were excluded (pediatric populations, type of HSCT was not mentioned and irrelevant reviews). I ended up with 36 studies. From these, I excluded three old original articles that were not found (with the librarian aid) and five studies where prevalence was given for both types of HSCT mixed, not only autologous.(The authors were contacted and only two replied that they have no primary data, the study was conducted 20 years ago).Two studies where BSI is only given for Vancomycin Resistant Enterococci (VRE), one study where BSI is only given for streptococcus Mitis, two irrelevant articles without any BSI prevalence, eight irrelevant reviews without any BSI prevalence, five studies where in the analysis they included pediatrics were all excluded. Ten final relevant studies remained for the meta-analysis (Figure1).

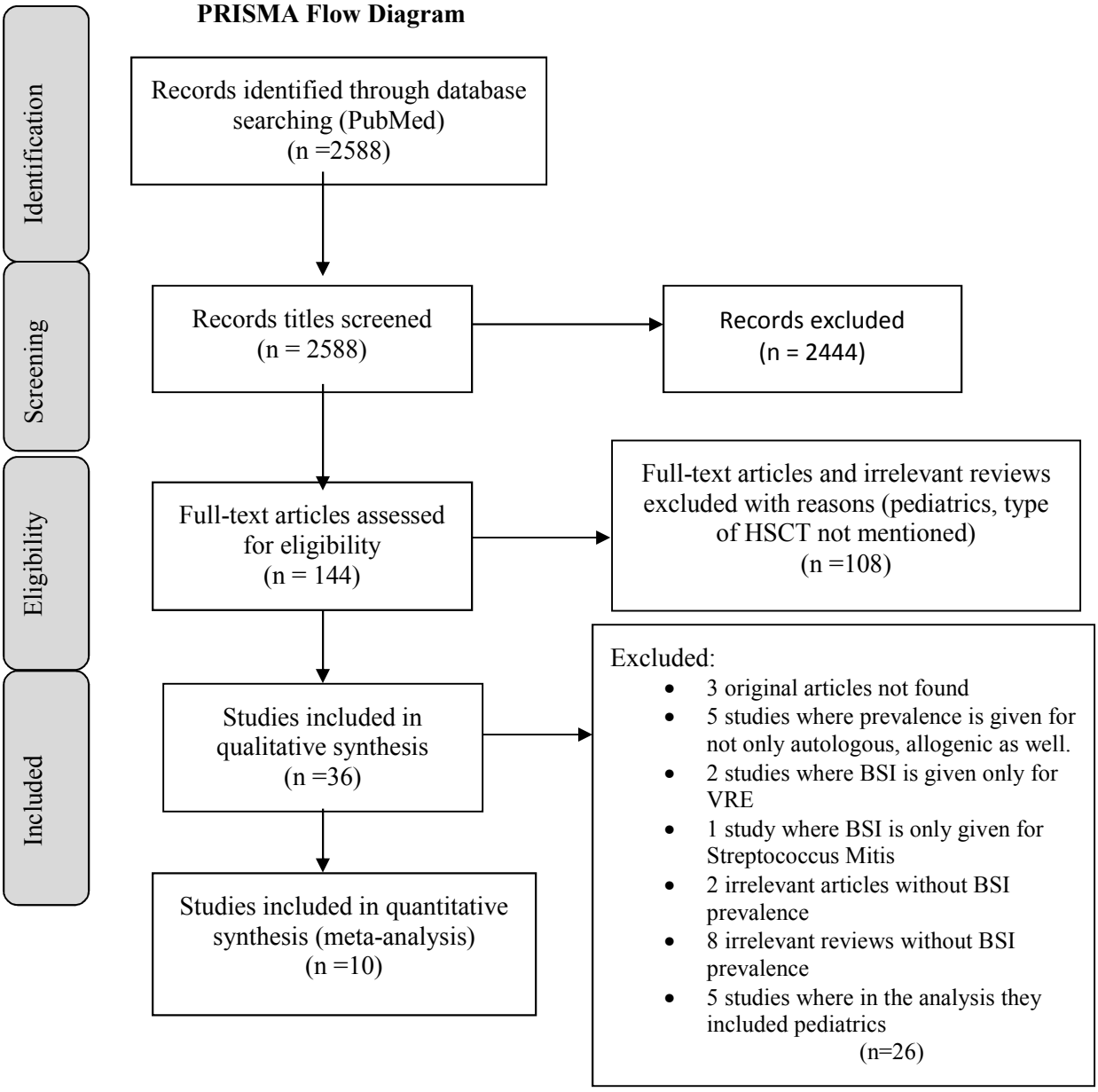

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart of the literature search conducted in January 2017 for the systematic review and meta-analysis.

Characteristics of the included studies

The population studied had 55789 patients aged 16 years and above who underwent autologous HSCT from the United States, France, Finland, Poland, Germany and India.

Median age in eight studies ranged from 36 to 56 years with one study reported to include patients with age more than 16 years old and the other to have an age range from 18 to 65 years old. The proportion of female subjects ranged from 22.7 % to 63.6% across all studies. Five studies were in the U.S while the other four were in different European countries and one in India. Included studies ranged from 1989 to 2008 with duration from 1 year to 14 years. Seven studies were nested case-control, whilst the others were cohort studies. Gagan et.al. had a very large sample size of 53,337 to Yi Kong-Keung et.al. with a sample size of only 11 patients. The rate of BSI using CDC definitions, ranged from 5.2% to 63.6 %. (Table4). The quality scores of the ten studies ranged from 4 to 8 out of a maximum of nine (Tables 5 and 6).

Table 4 Studies evaluating BSI according to CDC definitions, in AHSCT patients from 1989 to 2016

Author (year)	Country	Study period	Study type	Sample size	Age	Female (%)	Rate of BSI (%)
Gagan Kumar et.al (2015) (35)	U.S.	2000-2008	Nested case-control	53,337	18->65	43.4	5.2
Michael J. Satlin (2014) (36)	U.S.	2007-2011	Nested case-control	287	56(44-63)	Not reported	37.9
Lalit Kumar (2010) (37)	India	1995-2009	Nested case-control	44	35(15-67)	22.7	47.7
Sari Hamalainen (2009) (38)	Finland	1996-2006	Nested case-control	319	55(16-73)	40.7	21
L. Gil (2007) (39)	Poland	1994-2005	Nested case-control	314	36(16-67)	44.2	33.7
MH Miceli (2006) (40)	U.S.	1998-2002	Retrospective cohort	367	56(30-77)	38.6	19.8
M. Dettenkofer (2005) (41)	Germany	2003-2005	Prospective cohort	726	>16	Not reported	18.1
AA Toor (2001) (42)	U.S.	1996-1998	Retrospective cohort	107	46(14-63)	54.2	28
Nicolas Ketterer (1998) (43)	France	1989-1997	Nested case-control	277	48(15-68)	37.9	20.5
Y.Kong-Keung (1995) (44)	U.S.	1995	Nested case-control	11	46(31-62)	63.6	63.6

Table 5 Newcastle Ottawa Quality Assessment Scale for the cohort studies included in the meta-analysis

Author, publication year	Cohort representativeness	Case selection for non-exposed	Ascertainment of exposure	BSI not present at start	Assessment of outcome	Analysis adjusted for confounders	Total score (points)
MH.Miceli et al 2006	**2**	**1**	**1**	**1**	**0**	**1**	**6/9**
M. Dettenkofer et al 2005	**2**	**1**	**2**	**1**	**1**	**0**	**7/9**
AA. Toor et al 2001	**2**	**1**	**2**	**1**	**1**	**1**	**8/9**

Table 6 Newcastle Ottawa Quality Assessment Scale for the case-control studies included in the meta-analysis

Author, publication year	Definition of cases	cases Representativeness	Selection of controls	Analysis adjusted for confounders	Ascertainment of exposure	Definition of controls	Total score (points)
Gagan Kumar et.al 2015	**1**	**1**	**1**	**1**	**2**	**0**	**6/9**
M. Satlin et al 2014	**1**	**1**	**1**	**1**	**1**	**1**	**6/9**
L.Kumar et al 2010	**0**	**1**	**1**	**0**	**1**	**1**	**4/9**
S.Hamalainen et al 2009	**1**	**1**	**1**	**1**	**2**	**1**	**7/9**
L. Gil et al 2007	**0**	**1**	**1**	**1**	**1**	**0**	**4/9**
N.Ketterer et al 1998	**1**	**1**	**1**	**1**	**2**	**0**	**6/9**
Y.Kong-Keung et al 1995	**1**	**1**	**1**	**1**	**2**	**0**	**6/9**

Quantitative analysis

The aggregated results were reviewed in the 10 studies and illustrated in Figure (2). I obtained very close results in both IVhet (6%, 95% CI: 0, 33) and QE (10%, 95% CI: 0, 33). Significant heterogeneity was noted among the studies ($\boldsymbol{I}^2$ = 99%; $\boldsymbol{P}$ = 0.0001).

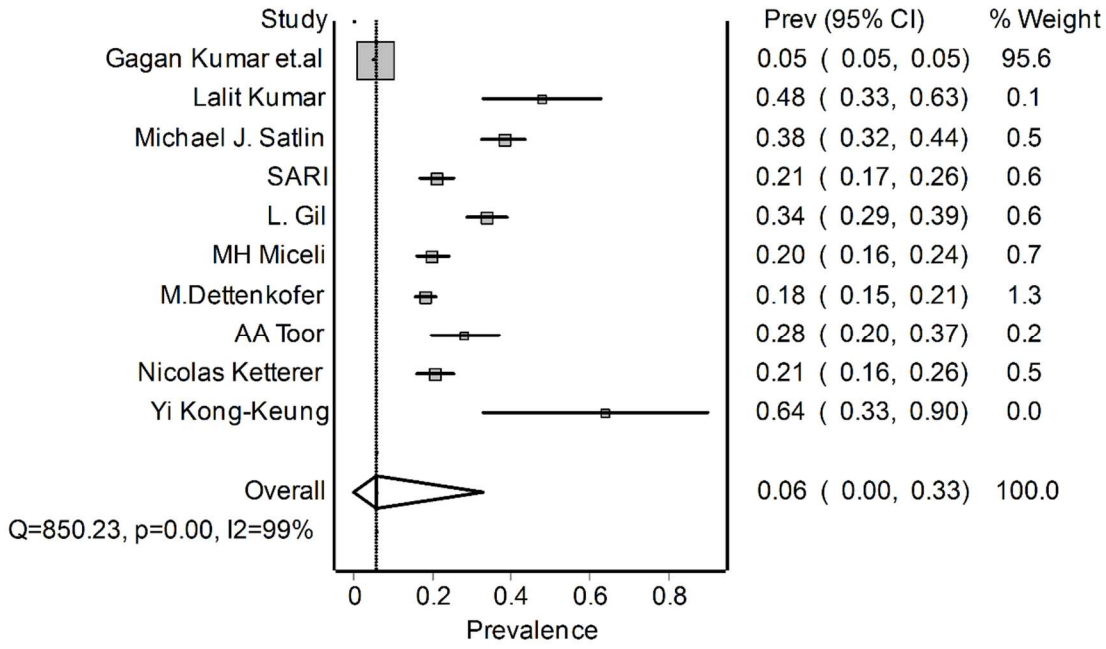

Figure 2. Forest plot with IVhet model

Subgroup analysis

Across the five studies conducted in America, the estimated prevalence of BSI was 5 % (95% CI 0%-36%), which was much lower than the estimated prevalence among European and Asian studies 23 % (95% CI 13%-34%). As the 95% CI overlap, no significance difference was observed.

Moreover, I stratified the studies based on the number of patients>200 and <200 and found that the estimated BSI prevalence was 6 times higher in studies with number of

participant>200. The Prevalence was 36 %, 95% CI 15%-58% and 6 %, 95% CI 0%-32% respectively. The stratification per antibiotic prophylaxis administration showed that with prophylaxis, the BSI prevalence was lower (Table 7).

Table 7 Subgroup analysis of the summary estimates

Bloodstream Infections	**Studies**	**N**	**Combined effect (95% CI)**	I^2
All studies	10	57789		
Studies≥200 patients	7	55627	36 %(15%-58%)	77%
Studies≤200 patients	3	2162	6 %(0%-32%)	99%
Geographic region				
America	5	54109	5 %(0%-36%)	99%
Europe and Asia	5	3680	23 %(13%-34%)	93%
Antibiotic prophylaxis	7	56733	6 %(0%-37%)	99%
No antibiotic prophylaxis	3	1056	19 %(0%-84%)	90%

Publication bias

The funnel plot of 10 studies using BSI prevalence as the outcome indicator was showed in Figures 3a and 3b. There was a significant asymmetry observed in the Doi and funnel plots, and an obvious publication bias (I^2 98.9%) was seen.

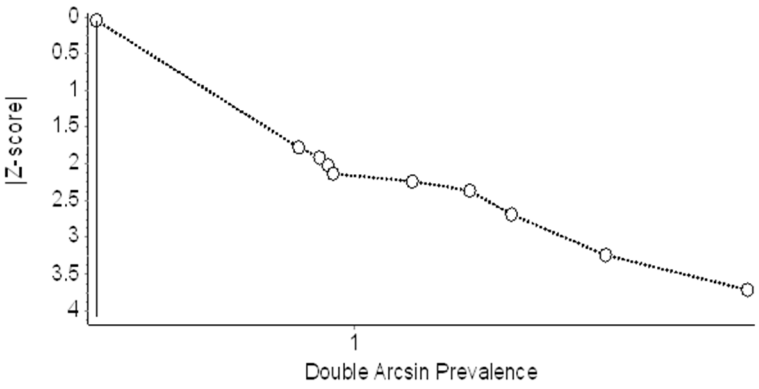

Figure 3a. Doi plot of all studies

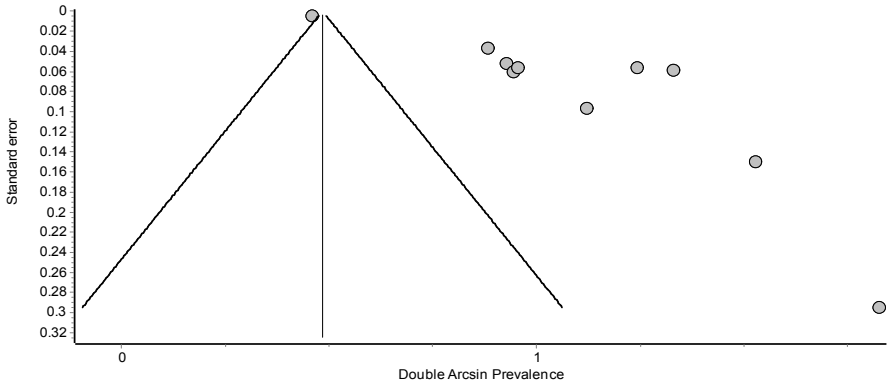

Figure 3b. Funnel plot of all studies

CHAPTER 5: DISCUSSION

In this single hospital, retrospective descriptive analysis for the period going from October 2015 to October 2016, looking at HAI after autologous hematopoietic stem cell transplant, I found that only18.75% of the patients had an infectious complication during their admission period. Diarrhea was one of the common complications and it was, most probably related to the high-dose chemotherapy regimens they were on (45).

The rate of microbiologically proven bacterial infections in our patients (12.75%) was comparable to that reported by others for autologous hematopoietic stem cell transplant. However, some authors have reported higher rates (40).

It has been well documented from several similar studies that bloodstream infections can be of a high prevalence after AHSCT, but such infections were not observed in my study. In contrast, I did not have a single case of bloodstream infection or sepsis. The low remarked prevalence of bloodstream infection might be attributable to the antimicrobials administered during preparation and immediately after AHSCT periods (14 patients received antibiotics (87.5%)) or due to the short duration of neutropenia (39). Neutropenia duration of more than 9 days is well known as the utmost risk factor for the occurrence of fungal infections and it is considered to be the single independent risk factor for bloodstream infection in the AHSCT patients (23) (40). I had a mean duration of neutropenia of 6.31 days. The prevalence of infections in the NCCCR HSCT unit compared with that in other populations, share many similarities with other published infection rates in patients post AHSCT. The NCCCR study showed no increase in BSI risk following the autologous transplant, it was not at all encountered and there was no

death occurrence. As for the meta-analysis, I found an overall prevalence of BSI of 6%.

Indeed, recipients of hematopoietic stem cell transplants are at a particular risk of bloodstream infection a large number of published studies addressed this association. Interestingly there was a remarkable distinction seen in the reported prevalence of BSI for studies having a large sample size, they had higher prevalence, this might be due to the unknown confounders like the difference in infection control measures implementation or the different level of care implemented in each of the settings.

There was as well a difference between the geographical locations; the studies conducted in America had an prevalence lower than the ones conducted in Europe and India this might be due to their well-established antibiotic stewardship guidelines as it was first implemented in the United States hospitals in 2006 by the Society of Healthcare Epidemiology of America (SHEA) (47). It was also noted that there was a 13% reduction in the prevalence of BSI when antibiotic prophylaxis was administered.

The main most important study limitation was its small sample size. I only had 16 patients who underwent the autologous transplantation during the study period.

Other limitations are the study's retrospective nature; all the information about the infections was procured retrospectively and the potential patients selection biases.

In this manner, given these restrictions, our data must be cautiously interpreted. The small sample size made the estimates of prevalence imprecise and this was demonstrated by the wide 95% CI.

In conclusion, this study provides original baseline data about the prevalence of HAI

among AHSCT in NCCCR. These findings will be used for further evaluation of the influence of infection prevention and control measures and therapeutic plans, including robust antibiotic stewardship well-functioning program for these patients for the purpose of contributing to the improvement of the quality of care in NCCCR, especially in the hematopoietic stem cell transplant unit (HSCT). In accordance with prior experience and study findings, our data is adding confirmation that most of hospital associated infections in AHSCT patients are acquired throughout neutropenia (19) (20) (22). Carrying on with surveillance and initiation of further studies involving hygiene measures and antibiotic use in hematologic stem cell transplantation units, are required to additionally assess the risk factors that contribute to severe infection in this category of patients. These findings may have implications for the clinical management of stem cell transplant recipients, one of them is to correct any deficiency found in medical records during the study, the second is with regards to optimizing prophylactic and treatment strategies in AHSCT recipients the third is to create a collaborative work to investigate HAIs among AHSCT in GCC countries. Evidence based infection control strategies should continue to be applied in the transplant unit leading subsequently to less hospital associated infections.

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APPENDIX A: DEFINITIONS

Healthcare Associated Infections (HAI): also, called nosocomial infections, are infections that patients acquire during receiving treatment for other conditions within a healthcare setting. They are defined as those that develop during hospitalization but are neither present nor incubating upon the patient's admission to the hospital; generally, for those infections that occur more than 48 to 72 hours after admission and within 10 days after hospital discharge (CDC 2004).

Hematopoietic Stem cell transplant (HSCT): is the intravenous infusion of hematopoietic stem and progenitor cells designed to establish marrow and immune function in patients with a variety of acquired and inherited malignant and nonmalignant disorders. These include hematologic malignancies (e.g., leukemia, lymphoma, and myeloma), nonmalignant acquired bone marrow disorders (e.g., aplastic anemia), and genetic diseases associated with abnormal hematopoiesis and function (thalassemia, sickle cell anemia, and severe combined immunodeficiency). HSCT is also used in the support of patients undergoing high-dose chemotherapy for the treatment of certain solid tumors for which hematologic toxicity would otherwise limit drug administration (germ cell tumors, and neuroblastoma).

Neutropenia is an abnormally low level of neutrophils. Neutrophils are a common type of white blood cell important to fighting off infections — particularly those caused by bacteria. For adults, counts of less than 1,500 neutrophils per microliter of blood are considered to be neutropenia.

ANC engraftment is defined as 3 consecutive days with an ANC (absolute neutrophil

count) of 0.5×10^9/L or 1 day with a count of 1.0×10^9/L.

Engraftment: Days 0-30. Is when the body accepts the transplanted bone marrow or stem cells and they begin to produce new blood cells and immune system cells. It is a step in a successful stem cell transplant.

APPENDIX B: DATA COLLECTION SHEET

Data collection sheet -Hematopoetic stem cell transplant case

Surveillance of Healthcare Associated Infections in Adult Recipients of Autologous Hematopoietic Stem-Cell Transplantation (AHSCT) at The National Center for Cancer Care and Research Qatar, a year after opening the transplant unit.

Please write inside number and date frames or place a cross in the appropriate box using a black pen

Abstractor's Initials

Abstractor's corporation number

Date of admission: .....mm .....dd.....yy

Admission type : Elective(1) Urgent(2)

Age : .....yy

Sex : Male(1) Female(2)

Nationality : Qatari(1) Other(2)

Diagnosis: Multiple myeloma(1) Plasmacytoma(2) Follicular lymphoma(3)

other 4(please write)

Date of HSCT .....mm .....dd.....yy

Date of discharge: .....mm .....dd.....yy

Death yes (1) No(2)

Comorbidity yes (1) No(2)

Comorbidity type Diabetes(1 HTA (2) Neutropenic (3)
Other(4)

Febrile neutropenia yes (1) No(2)

Duration of neutropenia .....dd

Date of infection .....mm .....dd.....yy

Invasive devices yes (1) No(2)

Type of intravascular device HL(1) PICC(2) other(3)

Type of urinary catheter FC(1) other(2)

Healthcare associated infection yes (1) No(2)

if yes ,Healthcare associated infection type :
BSI (1)
CLABSI (2)
CAUTI (3)
Pneumonia(4)
Gastroenteritis(5) Type
Cdifficile(6)
Mucositis(7)
Other(8)

Infection Non Healthcare associated				yes (1)	No(2)													
if yes ,type :																		
BSI (1)																		
CLABSI (2)																		
CAUTI (3)																		
Pneumonia(4)																		
Gastroenteritis(5)			Type															
Cdifficile(6)																		
Mucositis(7)																		
Other(8)																		
Pathogen causing the infection																		
Antimicrobial therapy			yes (1)	No(2)														
If yes,choose																		
Meropenem (1)	Cefuroxime(5)			Vancomycin(9)														
Azitromycin(2)	Co-trimoxazole(6)																	
Ciprofloxacin(3)	Cefepim(7)																	
Metronidazole(4)	Ceftriaxone(8)																	
Infection during neutropenia				yes (1)	No(2)													
Infection during 30 patient days				yes (1)	No(2)													
Infection during 100 patient days				yes (1)	No(2)													
Infection pre-engraftment period				yes (1)	No(2)													
Infection post-engraftment period				yes (1)	No(2)													

APPENDIX C: NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE CASE-CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
a) yes, with independent validation ⁻
b) yes, e.g. record linkage or based on self-reports
c) no description

2) Representativeness of the cases
a) consecutive or obviously representative series of cases ⁻
b) potential for selection biases or not stated

3) Selection of Controls
a) community controls ⁻
b) hospital controls
c) no description

4) Definition of Controls
a) no history of disease (endpoint) ⁻
b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
a) study controls for _____ (Select the most important factor.) ⁻
b) study controls for any additional factor ⁻ (This criterion could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
a) secure record (e.g. surgical records) ⁻
b) structured interview where blind to case/control status ⁻
c) interview not blinded to case/control status
d) written self-report or medical record only
e) no description

2) Same method of ascertainment for cases and controls
a) yes ⁻
b) no

3) Non-Response rate
a) same rate for both groups ⁻
b) non-respondents described
c) rate different and no designation

APPENDIX D: NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort

a) truly representative of the average _____ (describe) in the community ¯

b) somewhat representative of the average _____ in the community ¯

c) selected group of users e.g. nurses, volunteers

d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort

a) drawn from the same community as the exposed cohort ¯

b) drawn from a different source

c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure

a) secure record (e.g. surgical records) ¯

b) structured interview ¯

c) written self-report

d) no description

4) Demonstration that outcome of interest was not present at start of study

a) yes ¯

b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis

a) study controls for _____ (select the most important factor) ¯

b) study controls for any additional factor ¯ (This criterion could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome

a) independent blind assessment ¯

b) record linkage ¯

c) self-report

d) no description

2) Was follow-up long enough for outcomes to occur

a) yes (select an adequate follow up period for outcome of interest) ¯

b) no

3) Adequacy of follow up of cohorts

a) complete follow up - all subjects accounted for ¯

b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ¯

c) follow up rate < ____% (select an adequate %) and no description of those lost

d) no statement