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A New Insight into Nosocomial Infections: a Worldwide Crisis

Elham Sheykhsaran[1, 2, 3], Hamed Ebrahimzadeh Leylabadlo[6], Farbod Alinezhad[4, 5], Hadi Feizi[3, 4], Hossein Bannazadeh Baghi[1,2,4*]

[1]Infectious and Tropical Diseases Research Center, Tabriz University of Medical Sciences, 5166/15731 Tabriz, Iran; [2]Immunology Research Center, Tabriz University of Medical Sciences, 5166/15731 Tabriz, Iran; [3]Students' Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran; [4]Department of Bacteriology, Faculty of Medicine, Tabriz University of Medical Sciences, 5166/15731 Tabriz, Iran; [5]Drug Applied Research Center, Tabriz University of Medical Sciences, 5166/15731 Tabriz, Iran; [6]Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

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***Correspondence**
Email:manuscriptacademic@gmail.com
Tel: +984133364661
Fax: +984133364661

ABSTRACT

The term "Nosocomial" is attributed to the diseases acquired by the patient under medical care. Various microorganisms, including bacteria, viruses, and fungi, may contribute to developing nosocomial infections (NIs). Urinary tract infections (UTI), surgical-site infections (SSI), bloodstream infections (BSI), and pneumonia are the most well-known instances. We investigated various aspects of NIs and the main causative agents of NIs, particularly bacteria, antibiotic resistance, crucial viral infections in hospitals, and a brief survey of fungal infections. It was concluded that specific human body tissues such as those in the lungs and urinary tract are more likely to be a target for nosocomial pathogens. The fatalities associated with these infections, particularly in the intensive care unit (ICU), are serious concerns, and transmission by health facilities has become a primary medical issue because of its spread into the community. Another medical point is antibiotic resistance which is a leading cause of prolonged periods of hospitalization and makes the treatment procedure harder and costlier. Additionally, measures to prevent the spread of NIs and minimize the economic loss are discussed. All physicians and medical students must be updated about different kinds of these infections, their causative agents, challenges, and how to deal with them to reduce the consequences and improve public health.

INTRODUCTION

Nosocomial infections (NIs) affect hospitalized patients in all clinical centers and hospital wards [1]. NIs, as a global medical problem, account for about 7% and 10% of all infections in developed and developing countries [2]. Bacteria, viruses, and fungi are the underlying causes of hospital-acquired infections; however, bacteria are the main causative agents in 90% of cases [3]. Gram-negative bacilli and Gram-positive cocci are the most known bacterial, and *Aspergillus* spp., *Candida albicans*, and *Cryptococcus neoformans* are the primary fungal agents contributing to NIs. According to shreds of evidence, viruses may also contribute to some outbreaks [2, 4]. The infection rate in elderly patients, chemotherapy recipients, and patients with underlying diseases is higher than in healthy individuals [5]. Typically, 5-10% of patients in the ICU contract anywhere 1-5 types of NIs. Urinary tract infections (UTIs), surgical-site infections (SSIs), bloodstream infections (BSI), and pneumonia are the most broadly categorized types of NIs by the Centers for Disease Control and Prevention (CDC), which are involved in more than 80% of the cases. A hospitalized patient is more vulnerable to various microorganisms, notably bacteria. Alongside other Gram-positive and Gram-negative bacteria, *S. aureus* is an important cause of BSI, pneumonia, and SSI. Pulmonary infections are associated with *A. bumannii*, *L. pneumophila*, and *Pseudomonas aeruginosa*. The burn wards are colonized dominantly by *P. aeruginosa* and Methicillin-resistant *Staphylococcus aureus* (MRSA). Gram-negative bacilli contribute to all NIs with a certain proportion. The prevalence rate and involved tissues have been inserted in Table 1 [6-14]. NIs or health-care associated infections can be transmitted readily to non-patients in hospitals. The most well-known cases are included lower respiratory tract infections, lung abscess or empyema, bone and joint infections,

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cardiovascular infection, central nervous systems infection, and reproductive tract infections [15]. Approximately, 70% of infections caused by microorganisms are resistant to one or more antibiotic classes. The emergence of resistance is a crisis rooted in the indiscriminate prescription of antibiotics [16, 17]. Infections in the surgery wards are also challenging, with a third of patients contracting skin or wound infections post-surgery. The role of Gram-negative bacteria is prominent in comparison to the Gram-positives in these types of infections [7, 18]. Out of every 1000 hospitalized patients, seven are afflicted by *P. aeruginosa* infections, most often in burn wards. Children and elderly patients are at a greater risk of developing such infections [19]. The most remarkable consequences are prolonged hospitalization and economic losses [20]. Knowledge of the origin of causative agents and their transmission route is crucial to preventing NIs. [21]. An ongoing debate is the relative role of aerosol transmission in the hospital setting, especially in vulnerable groups such as children and immunocompromised patients. Studies on medical settings and procedures or equipment relevant to increased risks of aerosol generation are required to prevent and control nosocomial infections via the aerosol route [22]. Due to the importance of NIs, in the realm of health and economics, here, we review the essential features of NIs, particularly the considerable role of bacteria and antibiotic resistance, which is the main challenge in the treatment procedure.

Table 1. The main bacterial causatives in common NIs and their prevalence.

Infection	Involved bacteria	Prevalence
UTI	*Enterococcus* spp., *S. aureus, E. coli, Klebsiella pneumoniae*	42%
SSI	Gram-negative organisms, *S. aureus*	20%
BSI	coagulase-negative *Staphylococci* (CONs), *S. aureus*, *Enterococci*, Aerobic Gram-negative bacilli	5-10%
Pneumonia	*P.aeruginosa, Serratia marcescens, S. aureus, Klebsiella* spp., *Streptococcus pneumoniae, Acinetobacter* spp., *Enterobacter* spp., *E. coli, Enterococcus* spp., *Stenotrophomonas maltophilia*	15-20%
Miscellaneous organs	All mentioned bacteria	16%

Bacteria

The role of bacteria in the NIs is significant due to the considerable proportion and side consequences [3]. Here, we aimed to discuss the more well-known bacterial cases.

Enterobacteriaceae. *Enterobacteriaceae*, a heterogeneous group of Gram-negative bacilli, are considered the most critical causative bacterial agents of NIs [23, 24]. All members of this family may cause BSI, abdominal infections, and peritonitis. They are found mainly in the different hospital wards, particularly in the ICU [25, 26]. *Enterobacter* spp. are the primary etiologic agents in nosocomial pneumonia [27]. Vancomycin-resistant *Enterococcus* (VRE) is one of the most well-known examples. The infections caused by these bacteria lead to extended hospitalization and mortality rates [28]. The members of this genus are inherently resistant to aminopenicillins, cefazolin, and cefoxitin via producing chromosomal AmpC beta-lactamase enzymes [29]. The presence of VRE in ICU and oncology-hematology wards is a medical challenge, and management of the treatment of colonized and infected patients and VRE identification must be considered an emergency action [30]. Based on recent analysis, nosocomial VRE infections increase hospital costs compared to VSE (Vancomycin Sensitive Enterococcus) infections. Therefore, implementing control measures to prevent VRE transmission seems to be necessary [31]. Overall, the emergence of carbapenem-resistant *Enterobacteriaceae* (CRE) and beta-lactamase-producing types is a significant medical concern to physicians and clinical microbiologists due to the limited available antimicrobials choice [32, 33]. One of the most important bacteria in pediatric wards is extended-spectrum beta-lactamases (ESBLs)-producing *E. coli* [34]. The resistance rate to imipenem in nosocomial *E. coli* isolates is over 90%, and ESBL-producing *E. coli* in hospitals is a significant challenge [35]. Also, *E. coli* contributes to nosocomial UTI incidence [36].

Klebsiella spp., especially *Klebsiella pneumoniae*, is another major cause of nosocomial UTI [36]. The rapid spread of this pathogen in hospitals underscores its importance and the occurrence of NIs [6]. Due to antibiotic resistance, particularly to carbapenems, managing the *K. pneumoniae* infections is more complicated. In addition to UTIs, this bacterium accounts for other NIs such as septicemia [14]. Recently, a high carbapenem-resistant *K. pneumoniae* incidence in patients with invasive infections occurred in Europe and Asia [37, 38].

Serratia marcescens is an opportunistic nosocomial pathogen that contributes to UTIs with mild to severe symptoms. This bacterium also causes respiratory and biliary tract infections, peritonitis, wound infections, and intravenous catheter-related infections [39]. There is also a worrisome emergence of drug resistance related to this pathogen by various mechanisms [40, 41]. Resistance to penicillins in *Serratia* spp. is over 90%, and the alarming fatality rate associated with *S. marcescens* is ~41.6 % [42].

Pseudomonas aeruginosa. *P. aeruginosa* is a difficult-to-treat pathogen and is abundantly found in hospital equipment. Besides infections in immunocompromised patients, this extremely virulent pathogen may cause pulmonary infections in cystic fibrosis patients [43, 44]. It

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accounts for up to 11% of NIs, with a high ability to colonize a broad range of organs [13]. Ventilator-associated pneumonia is a significant NI caused by *P. aeruginosa* [45]. This infection commonly occurs during extracorporeal membrane oxygenation, frequently by multidrug-resistant (MDR) microorganisms, resulting in a poor prognosis [46]. This bacterium also causes life-threatening infections in burn wards [47]. Currently, *P. aeruginosa* has a leading role in hospital-acquired bacteremia, accounting for ~4% of all cases and the third leading cause of Gram-negative BSI [48]. *Pseudomonas* spp. exhibits a high level of resistance to most antibiotics, resulting in high mortality rates [49]. One of the antibiotic resistance pathways in this pathogen is the active efflux pump and change in porin channel expression. The most important of these pumps belongs to the RND (resistance nodulation cell division) family. In addition to a significant intrinsic resistance to antibiotics, *P. aeruginosa* can acquire resistance utilizing chromosomal mutations and acquiring antibiotic resistance genes [50-52]. Based on previous data, *P. aeruginosa* isolates from the respiratory tract are resistant to imipenem [53]. The mortality rates reach 40-50% in patients with burn wounds infected with *P. aeruginosa*, which are very difficult to treat. Preventing burn wound infections with this microorganism is much more preferable and cost-effective than treatment after acquired infections [54, 55].

Acinetobacter baumannii. *A. baumannii*, a Gram-negative and nonmotile microorganism, is the significant cause of NIs. MDR *A. baumannii* is increasingly associated with various epidemics and has become a significant concern in various hospitals worldwide [56]. Bacteremia, surgical wounds, and respiratory tract infections are other NIs caused by this bacterium [57]. In inpatient facilities, *A. baumannii* is also a problematic microorganism, particularly in the ICU [58]. This opportunistic bacterium may cause infections in immunocompromised individuals with circulatory/respiratory system insufficiency and is more resistant to antibiotics than *Enterobacteriaceae* members. Therefore, it must be considered a severe clinical threat to patients and health care [59]. Imipenem is one of the best choices for treating pneumonia caused by this bacterium [60]. *A. baumannii* is more commonly isolated from ventilators than *P. aeruginosa*; however, it is not the leading cause of pneumonia associated with ventilators and BSI. The mortality rate of infections caused by this bacterium is ~34% [61]. A large group of hydrolyzing enzymes, such as MBLs, IMP, VIM, and class D carbapenemase, are produced by resistant isolates. Porin channels are the primary resistance caused by beta-lactams. Furthermore, recent investigations revealed that the loss of outer membrane proteins is also involved in the resistance to beta-lactams [50, 62].

Staphylococcus aureus. *S. aureus* is a major human pathogen in healthcare-associated infections. It has severe outcomes in endocarditis and prosthetic device infections [63-65]. *S. aureus* strains, in particular, MRSA, are one of the most common causes of hospital-acquired infections with increased prevalence over the past decade [66]. Hospital burn wards are usually considered a source of MRSA infections [67]. MRSA is a global health threat and is believed to have emerged due to excessive antibiotic prescription patterns [68]. According to extensive reviews, *S. aureus* is mostly isolated from equipment in hospitals [66]. This organism may colonize a wide variety of body tissues from the skin to the respiratory tract, and the status of the patient's immunity system may exacerbate the infections [69, 70]. The mortality rate of SSIs reaches up to 6.7% [71] as the second most important NIs, which affects approximately 2-5% of surgery-subjected patients [2]. Other infections, including pneumonia, mediastinitis, and UTI, may also be caused by this pathogen [72]. Resistance to β-lactam antibiotics makes the treatment procedure more complex [63].

Importance of antibiotic resistance in nosocomial bacteria. NIs have been elevating due to excessive and improper use of broad-spectrum antibiotics, particularly in healthcare settings [13]. Patients with underlying diseases and immunocompromised individuals are more vulnerable to the complications of antibiotic-resistant microorganisms [73]. Every five minutes in South-East Asia, one child dies due to a lack of effective antibiotics [2]. This resistance is evident in the *Enterobacteriaceae* and *Pseudomonas* spp. [74, 75]. The importance of antibiotic resistance as a medical issue is not elucidated completely for all microorganisms and associated infections; resistance determinants have a diverse origin [64, 76-78]. Environmental factors in antibiotic resistance, including water and food contamination, are significant, especially in Gram-negative bacteria [65, 79]. Hospitals also provide optimal conditions for microorganisms to develop resistance to effective antibiotics [53].

Attention to resistance may provide more desirable results and success if directed to decrease the NIs incidence [80].

Viral NIs

Viral NIs appear more in respiratory and gastrointestinal forms in hospitalized individuals, particularly immunocompromised patients [81].

Viral respiratory Nis. Elderly patients and hospitalized children in pediatric wards are more exposed to viral NIs than others. Respiratory syncytial virus (RSV) is directly related to NIs in pediatric wards [82]. RSV infections account for high mortality rates in children with an underlying disease, and in elderly patients, it causes pneumonia and increases cardiac manifestations [83]. It is difficult to distinguish viral cases of pneumonia from bacterial ones; therefore, the exact details of viral cases are not accurate. However, specific

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viral diagnosis methods identified RSV and influenza viruses as the cause of pneumonia in the ICU wards [84]. Hospitalized patients' most critical respiratory pathogens are adenoviruses and influenza type B virus [85]. The viral respiratory tract infections (RTI) in Germany in the winter of 2012-2013 reached the highest observed during the past decade [86]. Nosocomial influenza outbreaks are frequent, particularly among the frail groups, while the control remains challenging. However, the actual statistics are underestimated [87, 88]. Vaccinating the staff could be the primary strategy to reduce the consequences of nosocomial influenza infections in cancerous patients [89]. The human coronavirus contributes to RTI in pediatric wards, which might affect the ward staff [90, 91]. A pandemic of this virus in 2019 brought many changes worldwide, including lifestyle and compliance with health regulations [91]. This pandemic has also placed a massive burden on healthcare providers and hospitals worldwide. Several reports indicated nosocomial SARS-CoV-2 (severe acute respiratory syndrome-Corona Virus-2) outbreaks, with 60% mortality rates; however, it can vary in different countries [92-94]. The reports indicate that SARS-CoV-2 is not spread only by airbornes, and other transmission routes are also involved. Nosocomial transmissions can be prevented by rigorous basic control measures, such as wearing surgical masks, hand hygiene, and environmental hygiene [95].

Viral gastrointestinal Nis. Acute NIs of the gastrointestinal tract are among the most common infectious diseases in hospitals [96]. A point-prevalence survey in 2011 estimated the nosocomial gastrointestinal infections rate at 17.1%; however, it varies in different regions [15]. Healthcare-associated gastroenteritis outbreaks are prevalent and increasingly recognized in clinics; however, detailed knowledge of epidemiology is lacking [97]. Rotavirus, norovirus, astrovirus, and adenovirus are the four significant viruses contributing to nosocomial gastroenteritis. Of note is that the role of rotavirus, especially in the outbreak of diarrhea in pediatric wards, is highly significant [98, 99]. The role of astrovirus is also remarkable in diarrheic children. The majority of nosocomial diarrhea causative viruses are acquired through the oral-fecal route. The prevention process primarily relies on controlling virus transmission, such as frequent handwashing with soap and water [100]. Advanced molecular diagnostic methods can recognize many more nosocomial viral infections previously unreported. Such infections include norovirus gastroenteritis [101].

Viral NIs in immunocompromised patients. Immunosuppressed and elderly patients with underlying chronic diseases are at a higher risk of viral NIs [86]. HIV-infected hospitalized patients, including those whose CD4 lymphocyte count is less than a threshold, are more susceptible to pulmonary infections than other groups [102]. Some studies revealed that HIV-infected patients diagnosed with HSV infection and non-Hodgkin's lymphoma are more predisposed to contract NIs [103]. There is a possibility of transmission of human T-cell lymphotropic virus III (HTLV III) among the hospital staff due to needle-stick errors. This virus is prevalent among HIV-infected patients [104]. Due to limited therapeutic options to deal with viral infections, the emergence of antiviral resistance is a more serious problem compared to antibiotic resistance to bacteria. Acyclovir and ganciclovir-resistant herpes isolates pose a substantial threat to immunocompromised patients, especially those with HIV [105].

Nosocomial HBV (Hepatitis B Virus) infection has been traditionally relevant to the transfusion of contaminated blood and its products. Multiple HBV outbreaks have been observed in pediatric oncology inpatient wards [106]. Numerous factors contribute to the increased risk of infection in cancer patients, including immunodeficiency, underlying malignancy, and cytostatic chemotherapy [107]. Vaccination programs and ongoing HBV screening in oncology and pediatric hematology wards must become the standard of care [106, 108]. The HCV (Hepatitis C virus) is another common nosocomial pathogen transmitted through blood transfusion, dialysis, and kidney transplantation in hospital wards (Fig. 1) [109]. The hospital staff contributes to the dissemination of this virus [110]. Transmission of viral pathogens through the staff is an evident challenge in hospitals. The most remarkable example points out one of the most dangerous viral infections, Ebola, which affected healthcare workers in the 2014 outbreak and prepared the conditions for spreading the virus into the community [111].

Fungal NIs

Numerous fungal outbreaks have occurred in hospital settings which are considered a serious threat to immunocompromised individuals. Construction and renovation activities lead to severe dust contamination and disperse large amounts of fungal spores. These activities are an independent risk factor for invasive fungal infections [112]. The advent of new technologies in surgery, bone marrow, and organ transplantation plays a significant role in the high incidence of fungal NIs. Immunocompromised patients, particularly HIV-infected individuals, cancerous patients, and premature neonates, are more vulnerable to fungal pathogens, presenting the extreme severity of these infections [113, 114]. Additionally, hospitalized patients under chemotherapy who suffer from neutropenia and malnutrition are more likely to contract hospital-acquired fungal infections [113]. *C. albicans*, as a nosocomial pathogen with the ability to survive on surfaces for up to 4 months, is the most well-known hospital fungal agent [115]. There is a higher chance of candidemia in immunocompromised patients (Fig. 2) [116]. According to some reports, *Candida* spp. especially *C. albicans* can cause local and systemic infections in hospitalized patients, the most

[DOI: 10.52547/JoMMID.10.2.64]

prevalent mucosal NI [117]. Also, some BSI cases might be induced by *C. albicans* [118]. *C. auris* is a multidrug-resistant yeast that has emerged to cause nosocomial outbreaks in several countries over the past three years. This microorganism causes serious invasive infections and probably spreads among patients. It can survive for months on hospital equipment [119]. Some reports highlight ongoing challenges due to misidentification of this healthcare-associated fungal pathogen and remarkable mortality rates [120]. Other fungal agents have a significant role in nosocomial pulmonary infections, such as *Cryptococcus* spp. and *Aspergillus* spp., causing high mortality rates [121]. *Aspergillus* spp. can infect the lung and sinus maxillaries in frail patients [112]. Mucorales, *Fusarium* spp., and other molds may also contribute to fungal infections in hospital wards [122]. In addition to the species mentioned above, *Trichosporon* spp., *Fusarium* spp., and *Mucor* spp. are the most isolated fungal agents In ICUs and transplant wards [123].

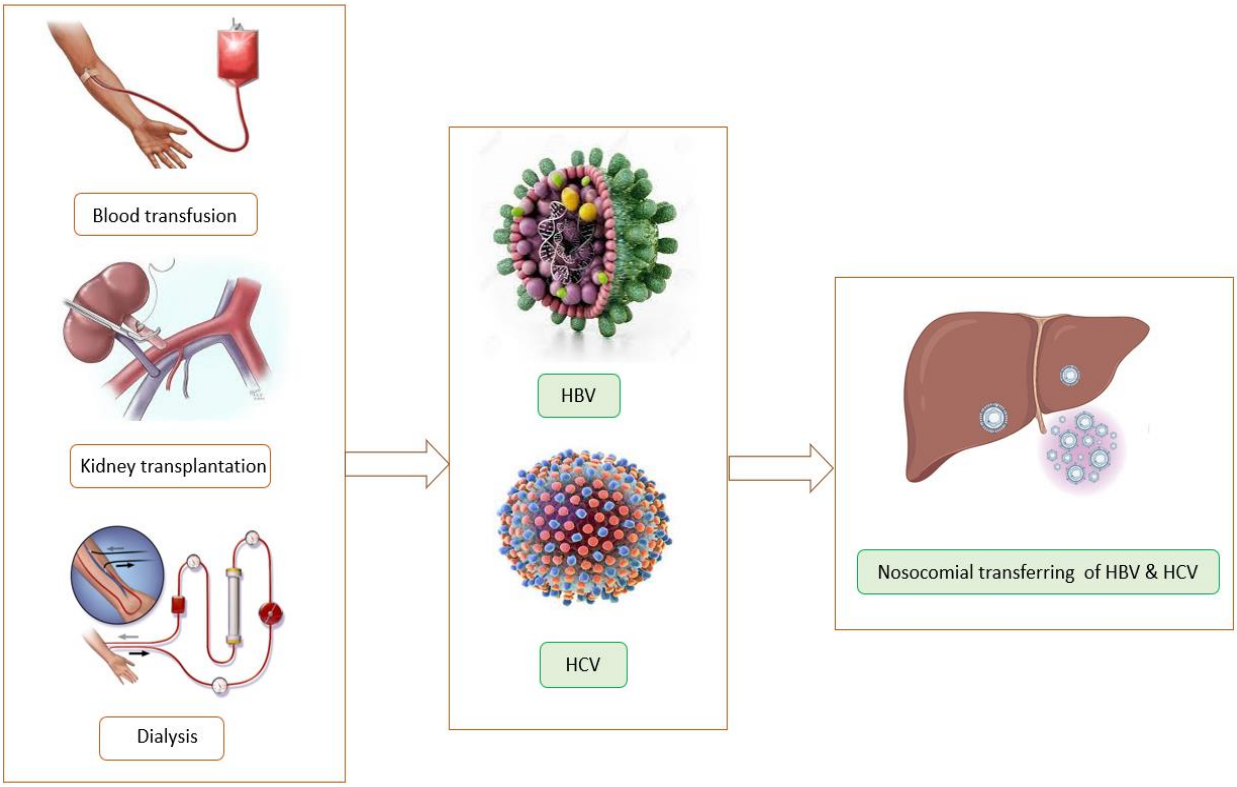

Fig. 1. Transmission routes of HCV and HBV in hospital wards. The HCV as a minor member of *Flaviviridae* is usually transmitted via blood transfusion from an HCV-infected patient. HBV can be transmitted readily through blood and related products in hospitals.

Impact of NIs on economy and society (how to deal with them)

The magnitude of hospital-acquired infections depends on the hospital area, hygiene circumstances, and hospitalization period. One of the most severe problems in dealing with these infections is antibiotic resistance [124]. The role of NIs in the mortality rate of hospitalized patients is tremendous. Even though the high morbidity rate in women is high, more mortality is observed in men [125]. Economic losses due to NIs consist of two critical aspects; increased treatment costs and extended hospitalization [126]. More than 7 million people in the United States see a physician due to the nosocomial UTI every year [127]. Apart from economic losses, which affect public health financially, extended hospitalization is another significant challenge (Table 2) [128-130].

With adequate staff training and observance of prevention and control regulations, the transmission of pathogenic agents associated with Nis can be controlled in hospitals and clinical centers [82]. Based on other published statistics, NIs affect more than 2 million people annually in the United States, with 90000 cases leading to death [16]. The concerns remain since resistant *E. coli* and *S. aureus* are the most commonly isolated bacteria from hospitalized patients. The role of microbiology laboratories will be momentous in identifying these pathogens and controlling them [53]. The primary measures to control NIs include several regulations which can effectively reduce these infections by up to 32% (Fig. 3) [16, 55, 131-133].

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Table 2. Economic loss and annually estimated mortality rate associated with NIs in the United States.

Type of nosocomial infection	Economic loss per case	Mortality rate	Excess Hospitalization
Urinary tract infections	558-593$	30.8%	1-4 days
Surgical site infections	2.734$	89%	7-8.2 days
Bloodstream infections	3.061-40000$	23.8-50%	7-21 days
Pneumonia	4.947$	14.8-71%	6.8-30 days

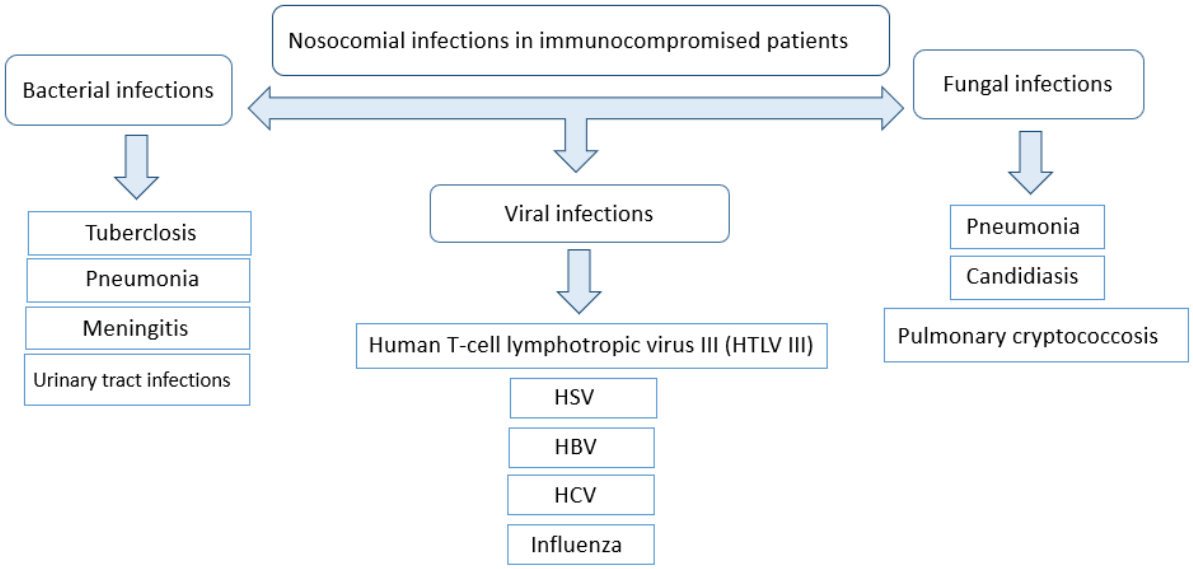

Fig. 2. NIs in immunocompromised patients. These individuals are affected readily by various microorganisms compared to healthy individuals and present more significant clinical symptoms.

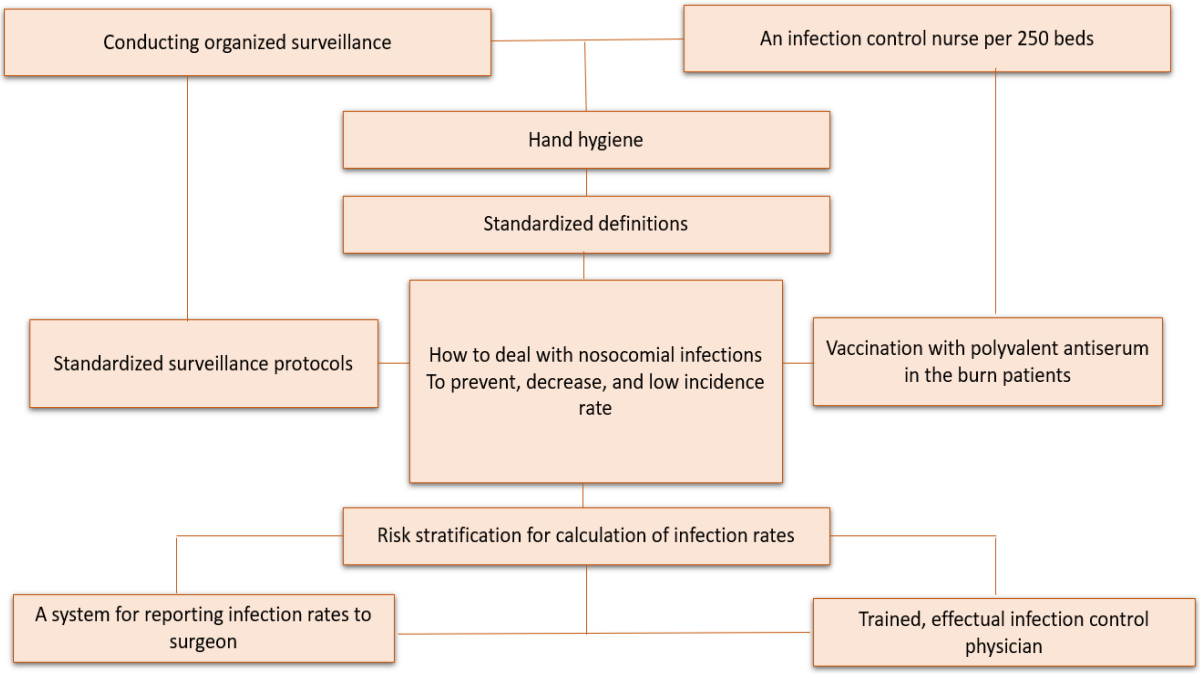

Fig. 3. Some recommended strategies by WHO for controlling NIs and reducing their incidence.

Conclusion

According to the published literature related to NIs, bacteria, viruses, and fungi have a significant role in the hospital infections incidence. Viruses and fungi may contribute to NIs, depending on the conditions. Viral infections mainly affect immunocompromised patients and pediatric wards. Immunocompromised individuals,

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especially HIV-infected patients and organ recipients, are the most vulnerable population groups. Bacteria, viruses, and fungi can cause coinfections, and overall, viral NIs have severe occurrence. The morbidity and mortality rate is variable in different age groups. Due to the emergence of antibiotic resistance, limited therapeutic options pose a severe health concern. Every microorganism presents different rates of antibiotic resistance, depending on multiple factors.

More studies on the impact of drug resistance in treating infectious diseases are required due to its impact on the health care system. It is urgent to implement practical solutions in hospitals and clinical centers to deal with these infections.

Concisely, NIs occur worldwide, and patients, communities, and health officials are involved in these infections directly or indirectly. Therefore, knowledge of the NIs must be updated continuously.

NIs surveillance is relevant to decreased infection rates, though randomized controlled trials require proving the influential role of surveillance. Decreased NIs incidences could shorten hospitalization time and reduce the financial burden. Therefore, hospitals may consider performing NIs surveillance systems according to their conditions**.** Besides the known nosocomial pathogens, emerging pathogenic agents are another serious issue that must be considered regarding resistance, treatment, and other medical aspects.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest associated with this manuscript.

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