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Review Article

Nosocomial Infections: A 360-degree Review

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It has been shown that nosocomial infections or hospital acquired infections are recurrent problems, identified chiefly in intensive care facilities, surgical, and medical wards. In Trinidad and Tobago information on nosocomial infections are lacking. Within the period 1992-1995, 7,158 nosocomial infections were documented from 72,532 patients (10.0/100 admissions). In Europe, incidences vary from 1% for all types of nosocomial infections and up to 23.6% in pediatric intensive care units. In the United States of America, the center for disease control and prevention calculated approximately 1.7 million nosocomial infections from all types of microorganisms resulting in 99,000 deaths annually. In this literature review we report the latest information on nosocomial infections affecting the skin and soft tissue, the urinary tract, the respiratory tract, bloodstream, and central nervous system. Risk factors, antibiotic resistance, and management of some infections are also discussed.

Keywords: Nosocomial infection, bacteria, antibiotic resistance, Trinidad and Tobago

It has been discovered that nosocomial infections or hospital acquired infections (HAIs) are recurrent problems, identified chiefly in intensive care facilities, surgical, and medical wards. There are numerous reports on this theme, e.g. in Europe, incidences vary from 1% for all types of nosocomial infections and up to 23.6% in pediatric intensive care units (ICUs) (1). Pediatric ICUs studies account for incidences between 6.1 - 15.1% (2, 3), while others in cross-sectional studies reported a prevalence of 11.9% and 33% (4, 5).

In the United States of America (USA), the center for disease control and prevention calculated approximately 1.7 million nosocomial infections from all types of microorganisms resulting in 99,000 deaths annually (6). U.S. hospitals, adjusted to include federal facilities, registered approximately 1.7 million infections among newborns, children, and adults in ICUs, and 1,266,851 among adults and children outside of ICUs. Deaths linked to HAIs in U.S. hospitals were 98,987. Of these, 35,967 were for pneumonia, 30,665 for bloodstream infections, and five-digit numbers for infections affecting the urinary tract and surgical sites (6).

More recently, health-care-associated infections declined for central-line associated bloodstream infections, surgical site infections, and methicillin-resistant *Staphylococcus aureus* (MRSA) infection, but the progress has been steady but slow for many of the priority health problems in the United States (7). According to data obtained from 47 French hospitals, a total of 12,188 *S. aureus* isolates and 6,370 *Pseudomonas aeruginosa* isolates were tested, and the incidence of resistant isolates had a stronger association with the rate of

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antimicrobial use (8). In Italy, from 2000, estimates retrieve approximately 6.7% nosocomial infection rate which resulted in 4,500 to 7,000 deaths, and a nosocomial infection rate of 4.9% (9).

In Trinidad and Tobago information on nosocomial infections are lacking. Within the period 1992-1995, 7,158 nosocomial infections were documented from 72,532 patients. High nosocomial infection rates were found on the intensive-care unit, neurosurgery, urology, surgery, and newborn nursery. Table 1 shows the rates of nosocomial infections in Trinidad and Tobago during 1992-1995. Urinary tract infections accounted for most nosocomial infections, followed by postoperative wound infections. Nosocomial pneumonias and bloodstream infections also were common (10).

It was reported that 1360 pediatric nosocomial urinary tract infections were identified from a total of 26,603 admissions during a five year retrospective chart review in a rural hospital in Trinidad and Tobago. The highest rate of infection per service per 100 admissions was seen in the nursery (11.28). *Escherichia coli, Proteus mirabilis, Klebsiella spp.* and group B *Streptococci* accounted for a total of 70% of all pathogens. The most effective antibiotics were nalidixic acid, gentamicin, and amoxicillin-clavulanic acid (11).

Again, in Trinidad and Tobago, from a nosocomial infection survey at a private hospital 139 hospital acquired infections were identified from 629 admissions to ICU. The nosocomial rate was 22.1%. In the ICU, the main nosocomial infections were from the respiratory tract, followed by surgical wounds, and urinary tract. From 165 bacterial organisms isolated, 80% were Gram negative bacilli, with *Pseudomonas aeruginosa*, being the most common isolate. The major Gram-positive isolates were *Staphylococcus aureus*, and many of them were methicillin- resistant. Resistance to ampicillin and augmentin was also alarming. Gentamicin, piperacillin-tazobactam and aztreonam resistance rates were also documented (12). These reports were from limited sources and there is therefore, a need to have comprehensive documented information on nosocomial infection from a wider number of health care facilities in Trinidad and Tobago. Table 1 reports on nosocomial infections at a rural hospital in Trinidad and Tobago.

Table 1. Rates of nosocomial infections at a rural hospital in Trinidad and Tobago during 1992-1995

Type of Nosocomial infection	Rates (%)
Urinary tract infections	42.0
Post-operative wound infections	26.8
Nosocomial pneumonias	13.2
Bloodstream infections	8.0
Others	10.0

Nosocomial Bloodstream Infections

Nosocomial bloodstream infection (BSI) is a principal infectious hurdle among seriously ill patients (13). In a study carried out in 17 countries in Western Europe it represented about 12%, and it was among the most frequent types of ICU infection reported (14). BSI acquired in the ICU are associated with significant morbidity and mortality. ICU infection preventions are including chlorhexidine body wash, central line bundles, and hand hygiene interventions (15). BSI occurred in closed to 85% of patients. *Enterococcus* (14%) and *Klebsiella* (14%) species were the most common organisms, and those patients with BSI had higher comorbidity scores and were more likely to be male, critically ill, on immunosuppression, and had a central venous catheter in place (16).

It has been reported that certain surgical or medical procedures may increase the probability of BSI, for example 35% of patients had an episode of the nosocomial BSI during venovenous extracorporeal membrane oxygenation (17-18). On the other hand, the effect of nosocomial bloodstream infections on mortality, length of stay, and hospital costs in older adults was studied. Among cases, the greatest percentage of BSIs were central line-associated, and *Staphylococcus aureus* was the most common pathogen accounting for 34.6% of

infections (2/3 were methicillin resistant). The mortality rate of cases was 49.4%, compared to 33.2% for controls, length of stay was 29.2 days for cases and 20.2 days for controls, and hospital charges were $102,276 for cases compared to $69,690 for controls. The mean length of stay and mean costs attributable to bloodstream infections were 10 days and $43,208, respectively (19).

Nosocomial skin and soft tissue infections

Nosocomial infections affecting the skin and soft tissues, include the clinical presentation of pain, edema, warmth, erythema, violaceous bullae, cutaneous blood loss, skin sloughing, skin anesthesia, rapid evolution, and gas in the tissue (20). Skin and soft tissue infections (SSTIs) result from invasion of the skin, and mostly occur due to trauma or surgery. SSTIs can be classified as simple, necrotizing or suppurative (21). Risk factors of acquiring SSTIs include older age, diabetes mellitus, immune-compromise, alcohol abuse, and prolonged hospitalization (22). The prevalence of SSTIs among inpatients is estimated at 7% to 10% (22-23). SSTI is one of the most frequent infections among inpatients, with increased frequency among men (22). *Staphylococus aureus, Pseudomonas aeruginosa, Enterococcus,* and *Escherichia coli* are commonly isolated from inpatients associated with SSTIs. Table 2 shows a considerable variation in the methicillin (oxacillin)-resistant *S. aureus* rate that was noted between countries and continents, with the overall rate highest in North America followed by Latin America and Europe (24-25).

Management of SSTIs is difficult owing to the variation of their presentation. The choice of antibiotic treament may be inconsistent and inefficient. Site of care is dependent on the severity of SSTI. Oral therapy is given to mild lesions whereas intravenous therapy is administered to moderate to severe lesions. The duration of treatment is determined by constant monitoring and clinical judgement (26-30).

Table 2. Causes of SSTIs (methicillin-resistant *S. aureus*) in different continents: report from the SENTRY Antimicrobial Surveillance Program (1998-2004)

Continents	Methicillin (oxacillin)-resistant *S. aureus* rate (%)
North America	35.9
Latino America	29.4
Europe	22.8
Others	11.9

Penicillin is given as first line treatment for group A *Streptococcus (Streptococcus pyogenes)* organisms identified from SSTIs. Alternative treatments for *Streptococcus pyogenes* include first generation cephalosporin, clindamycin, macrolides, glycopeptides or expanded spectrum fluoroquinolones. For SSTIs caused by group B *Streptococcus (Streptococcus algalactiae)* organisms first line high doses of penicillin G intravenously with clindamycin are adminstered. Cephalosporins, beta-lactamase inhibitors, cabapenems, fluoroquinolones or aminogylcosides are given to treat *Klbsiella pneumoniae, Eschericheria coli*, and *Serratia marcescens* identified from inpatients associated with SSTIs (23-25).

First line anti-pseudomonal beta lactam combined with aminoglycoside treatments are given for *Pseudomonas aeruginosa* identified isolates associated with SSTIs (31-32). Nowadays, the rates of MDR and extensively drug-resistant isolates amongst bacilli, particularly *Pseudomonas aeruginosa*, have risen worldwide. (33). Itani et al. conducted a study in 2011 to determine outcomes and costs of treating complicated SSTIs due to Gram-positive only, Gram-negative only, or mixed pathogens, including those with MRSA or *Pseudomonas aeruginosa*. Mixed pathogens incurred significantly higher length of stay, mortality, and charges than those infections by Gram-negative pathogens or to Gram-positive pathogens. *P. aeruginosa* cases had significantly higher length of stay and charges compared with patients infected with other microorganisms (34).

Nosocomial urinary tract infections (UTIs)

Catheter-associated urinary tract infections

(UTIs) are one of the most frequent types of nosocomial infection, and cause both increased patient morbidity and health care costs. Gram-negative opportunistic bacteria including *Klebsiella pneumoniae* is a prominent cause of nosocomial urinary infections in individuals with indwelling urinary catheters (35-36). The insertion of the catheter spreads the bacteria to the normally sterile bladder, and it is thought that the presence of an indwelling catheter becomes a site for bacterial attachment, and facilitates long-term colonization. Fimbria adhesins mediated attachment to host cell surfaces in Gram-negative enterobacteria (37). It has been shown that up to 80% of nosocomial infections are associated with indwelling medical devices and many of these types of infections can be predicted to be biofilm mediated (38-39). The insertion of these devices becomes a site for biofilm formation and downregulates some of the natural host immune defenses (40-41).

Although UTI is the most common nosocomial infection in the United States, there is not national data describing how hospitals in the United States prevent this patient safety problem. A national study was conducted to examine the current practices used by hospitals to prevent hospital-acquired UTIs. A survey that asked about practices to prevent nosocomial UTIs and other device-associated infections showed that 56% of hospitals lacked a system for monitoring patients with urinary catheters in placed, and 74% did not monitor catheter duration. The authors concluded that to prevent nosocomial UTIs, bladder ultrasound and antimicrobial catheters were each used in less than one-third of hospitals in USA (42). Michigan hospitals, compared with the rest of hospitals in USA, more frequently participated in collaboratives to prevent health care-associated infection (94% vs 67%, P <0.001), used bladder scanners (53% vs 39%, P = 0.04), in addition to catheter reminders or stop orders for nurse-initiated discontinuation (44% vs 23%, P <0.001). These preventive practices coincided with a 25% reduction in catheter-associated urinary tract infection in the state of Michigan, as compared with the 6% overall decrease observed in the rest of country (43-44).

The incidence of catheter-associated UTIs was 8.2% (189/2283 patients who had urinary catheter) in a study carried out in Spain. The most frequently isolated pathogens were *Escherichia coli*, followed by *Enterococcus spp* and *Pseudomonas aeruginosa*. *E. coli* showed resistance rates of 41.9% for quinolones, 33.3% of them produced extended spectrum B-lactamase. *P. aeruginosa* showed resistance rates of 42.1% for quinolones and 21.1% for carbapenems. Catheter-associated UTIs have a higher incidence of pathogens with antibiotic resistances and non-common pathogens (45).

Risk factors for catheter-associated UTIs include diabetes mellitus, urolithiasis, among others. In a Spanish study it was reported that 457 patients were hospitalized. Of them, nearly 12% have had a previous UTI. The most frequently isolated pathogens were *E. Escherichia coli*, followed by *Klebsiella*, *Enterococcus spp*, and *Pseudomonas* in another study carried out in Spain. Enterobacteriaceae other than *E. coli* were more prevalent in male and older patients. The prevalent nosocomial pathogen found in urinary catheters was *Enterococcus*. The resistance rates *E. coli* against ampicillin/amoxicillin + β lactamase inhibitor was 23.5%, 16.6% against third-generation cephalosporins, 31.3% against fluoroquinolones, and 16.7% against aminoglycosides. 11.4% of *Escherichia coli* strains were producers of extended-spectrum beta-lactamases. The resistance rates of *Pseudomonas* and *Enterococcus* against quinolones were 50.0% and 61.5%, respectively (46).

The first-line empiric treatment for acute uncomplicated bacterial cystitis in healthy adult non-pregnant females is a 5-day course of nitro-furantoin or a 3-g single dose of fosfomycin tromethamine. Second-line treatment include fluoroquinolones and β-lactams, including amoxicillin-clavulanate. Current therapy for UTIs due to AmpC- β -lactamase-producing pathogen

include nitrofurantoin, fosfomycin, fluoroquinolones, piperacillin-tazobactam, cefepime and carbapenems. In addition, therapy options for UTIs due to extended-spectrum beta-lactamases (ESBL) - producing Enterobacteriaceae include fosfomycin, fluoroquinolones, nitrofurantoin, cefoxitin, piperacillin-tazobactam, carbapenems, ceftazidime-avibactam, aminoglycosides and ceftolozane-tazobactam.

Taking in consideration the identification and susceptibility results, alternatives to carbapenems can be used in the treatment of mild-moderate UTIs caused by ESBL-producing Enterobacteriaceae. Colistin, ceftazidime-avibactam, polymyxin B, aztreonam, fosfomycin, tigecycline, and aminoglycosides are therapeutic options for UTIs caused by carbapenem-resistant Enterobacteriaceae. Therapy options for UTIs caused by MDR-*Pseudomonas spp*. include fluoroquinolones, cefepime, piperacillin-tazobactam, ceftazidime, carbapenems, aminoglycosides, ceftazidime-avibactam, colistin, and ceftolozane-tazobactam. The use of fluoroquinolones for empiric therapy of UTIs should be restricted due to increased rates of resistance. Aminoglycosides, tigecycline, and colistin should be considered alternatives in the setting of MDR Gram-negative infections in patients with scanty therapeutic options (47).

Nosocomial respiratory tract infections

Nosocomial respiratory tract infections are major causes of extreme morbidity and mortality in United States of America hospitals, affecting about five to ten of every 1,000 patients. Bacterial pneumonia accounts for 25% of all ICU infections. Ventilated acquired pneumonia is the highest in the initial course of hospital stay. Intubation and mechanical ventilation increases the risk of nosocomial respiratory infections (48). Among the 820 recorded episodes of HAIs, the most frequent type was lower respiratory tract infection (2.7 infections per 100 patients; 26.7% of all infections) in a study carried out in Greece (49).

The development of nosocomial respiratory tract infection is dependent on two independent pathophysiological factors: decreased immunity, and colonization of human cavities by bacteria (50). Need for mechanical ventilation, lymphocytopenia, sepsis, ICU admission on first day, older age and anemia were independent risk factors that predispose patients with severe influenza A (H1N1) pdm09 to nosocomial infection (51). Aspiration of nose and throat secretions is thought to be the most important cause of nosocomial respiratory infections, and dental plaques can also cause it (52). Nosocomial respiratory tract infections were commonly due to *Acinetobacter baumannii, Pseudomonas aeruginosa, Stenotrophomonas maltophilia*, and *Staphylococcus aureus* in a study performed in China (51).

Nosocomial respiratory infections can be treated with erythromycin or fluoroquinolone for cases of legionellosis. The following antibiotics are also given when treating nosocomial respiratory infections: amoxicillin with clavulanic acid, ceftazidime, imipenem, and piperacillin/tazobactam (48). It was observed that anti-microbial resistance had significant impact on the daily risk of 90-day mortality, which was increased by 90%-110% in patients infected by carbapenem-resistant Gram-negative pathogens (49, 53). A study exposed that nebulized amikacin showed better clinical outcome rates, less ICU stay, and quicker complete recovery compared to intravenous amikacin in post-cardiothoracic surgical patients with nosocomial pneumonia caused by MDR Gram-negative bacilli (54).

The emergence of ceftolozane-tazobactam resistance during MDR-*Pseudomonas aeruginosa* in nosocomial respiratory tract infections has been reported, and it is associated with increased mortality (55). Jauneikaite et al. reported an outbreak of a drug-resistant *Streptococcus pneumoniae* in an adult respiratory medicine ward, they were serotype 9V and had similar antibiotic susceptibility patterns. They were intermediate to penicillin, and resistant to erythromycin and

tetracycline (56). In addition, infections by MDR Gram-negative bacilli, including *E coli* and *Klebsiella pneumoniae* in neonatal intensive care units are increasingly reported (57).

We do not want to finish this section without mentioning the promising Telavancin (TD-6424), a semisynthetic lipoglycopeptide vancomycin-derivative, that is a novel antimicrobial agent developed for overcoming resistant Gram-positive bacterial infections, specifically MRSA, and has been successfully used in the treatment of various types of nosocomial infections caused by MDR Gram-positive bacteria e.g. *S. aureus, Streptococcus agalactiae, Streptococcus pyogenes,* and *Streptococcus anginosus* group. Telavancin is excreted mainly in the urine. Adverse effects include renal dysfunction and QTc prolongation. Due to its high binding capacity to plasma proteins, it expresses a long half-life (58). Clinical trials showed its safety and efficacy compared to vancomycin for the management of nosocomial pneumonia (59).

Nosocomial central nervous system infections

Like the other types of nosocomial infections, those involving the central nervous system (CNS) are associated with increased morbidity and mortality (60). These infections can rise from superficial wounds, foreign bodies (ventricular shunts), and the deep structures of the brain parenchyma. Most of nosocomial CNS are from bacterial meningitis and CNS shunt infections (60). 40% of bacterial meningitis infections are nosocomial, and Gram-negative bacilli (other than *Haemophilus influenzae*) caused 33% of the nosocomial episodes (61).

Nosocomial CNS infections can be divided into surgical or device-related, and non-surgical related infections. *Mycoplasma hominis* is an atypical pathogen that have been reported in the literature as a microorganism that causes nosocomial meningitis after surgical procedure in the brain. It is undetectable by Gram staining, and resistant to beta-lactam antibiotics (62-64). A case report showed the successful treatment of infection by *M. hominis* that was achieved after 6 weeks of clindamycin and ciprofloxacin administration, in addition to other procedures. It is important to consider *M. hominis* as the atypical pathogen, when beta-lactam antibiotics are ineffective and Gram staining is negative (65).

In most of recent studies published, from case reviews of nosocomial meningitis, frequent organisms observed as a cause of these infections were *Escherichia coli, Klebsiella spp., Pseudomonas, Acinetobacter, Enterobacter,* and *Serratia* organisms. Other organisms observed to cause nosocomial meningitis included *Staphylococcus aureus,* coagulase negative *Staphylococci, Streptococcus pneumonia,* and other *Streptococci* (66). Species of *Corynebacterium, Propionibacterium, Haemophilus, Listeria, Bacillus, Clostridium, Neisseria, Yersinia, Mycobacteria, Cryptococcus,* and *Ascaris* have the capability to cause nosocomial shunt infections (60).

In fact, CNS infections caused by pathogens with a reduced sensitivity to drugs are a therapeutic challenge, for instance, infections caused by penicillin-resistant *Pneumococci,* methicillin-resistant *Staphylococci,* multi-resistant Gram-negative aerobic bacilli, or several other organisms, including *Aspergillus* spp., *Scedosporium apiospermum,* and *Nocardia asteroids,* that affect primarily the CNS in immunocompromised patients. In addition, several antimicrobials including isoniazid, pyrazinamide, linezolid, metronidazole, fluconazole, and some fluoroquinolones are extremely valuable for the treatment of CNS infections (67). Daptomycin, fluoroquinolones, and tetracyclines have demonstrated favorable CNS penetration in adults, and macrolides and clindamycin have demonstrated poor CNS penetration in adults (68).

Finally, CNS drug penetration is influenced by the nature and extent of the infection. In children, antibiotics with good CNS penetration are intrathecal gentamicin and penicillins. Cephalosporins include cefuroxime, ceftriaxone, cefotaxime,

ceftazidime, cefixime, and cefepime. However, imipenem reaches higher CSF concentrations, and has lower frequency of seizures. Both chloramphenicol and sulfamethoxazole/trimethoprim (cotrimoxazole) penetrate the CNS well. Other antimicrobials that reach well the CNS include linezolid and rifampicin. Aminoglycosides and vancomycin have poor CNS penetration. No specific data are available for clindamycin, daptomycin, macrolides, tetracyclines, and fluoroquinolones in children (68). Table 3 shows microorganisms involved in nosocomial infections reported in several studies.

Table 3. Microorganisms involved in nosocomial infections reported by several studies

Type of nosocomial infection	Frequent pathogens involved in nosocomial infection	References
Bloodstream	*Enterococcus*, *Klebsiella*, and Methicillin-resistant *S. aureus*	[17, 20]
Skin and soft tissue	*Streptococcus pyogenes*, *Streptococcus algalactiae*, *Klebsiella pneumoniae*, *E. coli*, and *S. aureus*.	[24-26]
Urinary tract	*E. coli*, *Klebsiella spp*, *Pseudomonas*, and *Enterococcus*	[46, 47]
Respiratory tract	*S. maltophilia*, *S. aureus*, *E coli*, *A. baumannii*, and *K. pneumoniae*	[52, 58]
Central nervous system	*H. influenzae*, *E coli*, *Klebsiella spp*, *Aspergillus spp*, *Scedosporium apiospermum*, and *Nocardia asteroids*	[61, 67, 69]

Conclusion

Surveillance of nosocomial infections is important to reduce hospital stay, cost, and quality of life. In addition, carrying out prevention and control measures to reduce morbidity and mortality in the hospital is mandatory.

Conflict of interest

The authors declare that they have no competing interest.

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