Chapter 10
Recent Evidences in the Management of Nosocomial Infections

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INTRODUCTION
Nosocomial infection (NI), better known as hospital-acquired infection (HAI) is defined as an infection developing in hospitalized patients which is not present or incubating at the time of their admission. Nosocomial infection may also appear after discharge of the patient. Nosocomial infections are an unwelcome cause of patient’s morbidity and mortality at the hands of highly resistant microbes and by prolonging hospitalization, add significantly to the economic burden of the society. It is among the most difficult problems confronting clinicians who deal with severely ill patients. The incidence of NI is estimated at 5–10% in tertiary care hospitals reaching up to 28% in intensive care unit (ICU) in developing nations.

Ninety percent of the NIs is caused by bacteria, whereas mycobacterial, viral, fungal or protozoal agents are less commonly involved. Klebsiella pneumoniae, Staphylococcus aureus, Escherichia coli, Proteus spp. and Pseudomonas aeruginosa are among the most common causative agents of NI. Indiscriminate and over enthusiastic usage of broad-spectrum antibiotics in hospital environment promoted the emergence of newer organisms such as Acinetobacter baumannii, Burkholderia cepacia and Stenotrophomonas maltophilia.1-5

TYPES OF NOSOCOMIAL INFECTION
Though any organ system may be involved, but four infections are most common as external device is put or a breach in the integrity of skin is involved. These are:
2. Ventilator-associated pneumonia (VAP).
3. Central line-associated bloodstream infection (CLABSI).
4. Surgical site infection (SSI) and skin and soft-tissue infections (SSTI).

EPIDEMIOLOGY
Recent surveys on NIs have pointed out the significant changes in microbial flora and their distribution in various parts of the body.5

SOURCES OF NOSOCOMIAL INFECTION
- Endogenous: It is caused by microorganisms from patient’s own flora
- Exogenous: It is caused by microorganisms acquired by exposure to another patient, hospital personnel, visitor, medical devices and/or hospital environment.

Factors predisposing to nosocomial infection: They are as follows:
- Susceptible host (advanced age, immunosuppression, malnutrition and incapacitation)
- Inanimate hospital environment comprising of soiled linen, biomedical waste, used equipments and instruments congenial for microbial growth
- Invasive diagnostic and therapeutic procedures and long surgical procedures.

An interplay between these factors culminates in NI.

CHANGES IN MICROBIAL FLORA
The distribution of pathogens responsible for NI has changed over the years. The introduction of penicillin, which heralded the antibiotic era banished cases of severe sepsis mainly caused by S. aureus. Then as Staphylococci became beta-lactamase producers, beta-lactamase stable compounds controlled them. Then methicillin-resistant S. aureus (MRSA) and Gram-negative bacilli emerged as agents responsible for NI. In the late 1960s, resistant bacteria belonging to family enterobacteriaceae (Klebsiella spp., Escherichia spp., Proteus spp.),7 became increasingly involved in NI and in the years 1975–80, the emergence of multiresistant Gram-negative bacilli P. aeruginosa and Acinetobacter spp. was observed, presenting difficult therapeutic problems.6,10

More recent surveys have indicated the reemergence of Gram-positive cocci including coagulase-positive Staphylococci, coagulase-negative Staphylococci (C-NS) and Streptococci, whereas incidence of E. coli and K. pneumoniae has decreased from 23% to 16% and from 7% to 5% respectively.11,12 In addition, all surveys report the increasing or simultaneous persistence of P. aeruginosa, Acinetobacter spp. and emergence of newer nosocomial Gram-negative organisms such as B. cepacia and S. maltophilia.13,14

DISTRIBUTION OF PATHOGENS IN SPECIFIC SITES
In CAUTI, E. coli, Klebsiella spp., Proteus spp. and Streptococcus faecalis predominate while in VAP, P. aeruginosa and S. aureus are the leading pathogens. In SSI, SSTI and burns, Staphylococci and Enterococci are the leading pathogens respectively.
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**STRATEGIES FOR MANAGEMENT OF NOSOCOMIAL INFECTION**

Many antimicrobial agents are available today and antibiotic therapy should theoretically be chosen when the infecting organism and its susceptibility has been established in a given infection. More frequently and particularly in the ICU, antibiotic therapy is empirical because of emergency situations, severity of infections in immunodepressed, neutropenic and elderly patients, so optimal therapy in those difficult to treat situations should take into account the local microbiological backgrounds and their current resistance pattern. The most appropriate empiric treatment is best achieved on the basis of resistance surveillance.

The choice of empiric antibiotic therapy for the treatment of any NI before microbiology requires:
- Surveillance data on a regular basis of predominant organisms in the hospital/ICU
- Surveillance of the current resistance patterns of these organisms
- Identification of outbreaks of NI involving one or more prevalent organisms.

**PRINCIPLES OF EMPIRIC THERAPY**

The conventional empiric therapy which is started before culture reports arrive has to be broad enough to ensure coverage of most of the suspected pathogens. Combination therapy with antipseudomonal penicillin (piperacillin) plus aminoglycoside or an antipseudomonal cephalosporin (cefazidime) plus an aminoglycoside have been for long the initial regimen recommended officially. However, in situations suggestive of Gram-positive organisms such as MRSA, the addition of a glycopeptide forms part of empiric therapy. Rifampicin, fusidic acid, streptogramins (quinupristin-dalfopristin) also cover most Gram-positive organisms. During outbreaks of NI with high probability of cross-contamination of a previously identified endemic multiresistant organism such as *P. aeruginosa*, carbapenems (e.g. imipenem or meropenem) in combination with either an aminoglycoside (amikacin) or a fluoroquinolone (ciprofloxacin) should be recommended.

**Escalation/De-escalation**

Any empirical therapy should be reassessed 2 or 3 days after its initiation. Treatment should be readjusted on the basis of report of antibiotic sensitivity tests available on day 2 or 3 and clinical response of the patient. Potential choice of more suitable combination therapy or switch to less expensive/toxic antibiotics when the clinical status of patient suggests to do so is recommended.

**SPECIFIC EMPIRIC SITUATIONS**

- When anaerobic bacteria are suspected for instance in surgical abdominal polymicrobial infection or in aspiration pneumonia, the addition of clindamycin or cefoxitin or metronidazole is recommended. Imipenem is a useful alternative for mixed aerobic-anaerobic infections.
- If legionellosis is suspected (atypical pneumonia), erythromycin and rifampicin either alone or in combination are the antibiotics of choice.16
- In patients of neutropenia with neutrophil count 500/m3 or below and fever 38.3°C.

**INITIAL ANTIBIOTIC THERAPY**

- Cefazidime plus vancomycin. Vancomycin is given only if suspected causative agent is MRSA penicillin-resistant pneumococci or other Gram-positive resistant organisms.
- If vancomycin is not required then monotherapy with cefazidime, imipenem, ceftazidime or meropenem is given.
- If a combination is needed, standard combination should be cefazidime plus antipseudomonal penicillin (like piperacillin).17,18

**THERAPEUTIC STRATEGIES OF DOCUMENTED NOSOCOMIAL INFECTION**

The identification of the etiological agents involved in a given outbreak of NI should rely on an efficient clinical microbiology laboratory and good epidemiology practices within the hospital setup. Moreover, the choice of single agent or a combination of antibiotics based on clinical consideration should also refer to the known patterns of susceptibility/resistance (Table 1).19

The patient’s condition, severity of underlying disease, the presence of various devices (catheters, ventilator equipment, prosthesis, etc.) are important factors which may interfere with the choice of a single agent or a combination of antibiotics guided by the clinical condition of the patient.

The site of NI and pharmacokinetic consideration are other factors leading to an appropriate choice of antibiotics: adequate delivery of drug(s) in infected tissues depends on dosage and route of administration, and on local factors at the infection site such as potential inactivation of aminoglycoside at low pH, high protein binding with limited amount of free drug, poor penetration [e.g. cerebrospinal fluid (CSF)] and variable penetration of drugs into cells (macrophages) to reach and kill intracellular organisms (*Legionella pneumophila*).

**Choice of Antibiotics**

Most retrospective studies have concluded that combination therapy is superior to monotherapy. When combination therapy is decided by the clinician, the synergy of selected combinations must be examined.

**ANTIBIOTIC THERAPY IN SELECTED NOSOCOMIAL INFECTIONS**

**Nosocomial Pneumonia**

Pneumonia is the second most common NI and is associated with substantial morbidity and mortality. The common causative agents are: *P. aeruginosa*, *K. pneumoniae*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *E. coli*, *Moraxella catarrhalis* and *S. aureus*. The lung parenchyma and bronchial tissues are generally accessible to penicillins, third-generation cephalosporins and fluoroquinolones at concentrations high enough to inhibit most organisms. However, the multiple mechanism of resistance exhibited by two major pathogenic organisms, *P. aeruginosa* and S. aureus impose the use of combination of synergistic antibiotics—β-lactam and aminoglycoside. A specific problem is S. aureus strains with reduced vancomycin susceptibility.4 This leads to increased use of newer compounds such as quinupristin and dalfopristin. In addition although less frequently isolated from nosocomial pneumonia S. pneumoniae has become a worldwide problem because of its increasing resistance to penicillin and to most β-lactam antibiotics. This can be solved by using high dose of benzylpenicillin or with third-generation cephalosporins (ceftriaxone) or more recently developed drugs like cefpirome and cefepime. These antibiotics reach high lung parenchymal concent-ration up to 57.4 ± 13 ng/kg for ceftriaxone and high levels are also found in epithelial lining fluid and in bronchial mucosa. Specific conditions such as severe *Pseudomonas* nosocomial pneumonia or superinfection in cystic fibrosis patients may require achievement of higher tissue concentrations.

**Bacteremia: Nosocomial Bloodstream Infection**

There are several sources of bacteremic extension, mainly nosocomial pneumonia and UTI. Other foci of infection such as SSTI
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**TABLE 1 | Therapeutic strategies for management of nosocomial infections**

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Monotherapy</th>
<th>Combination therapy</th>
<th>Alternative therapy</th>
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<tbody>
<tr>
<td><strong>Gram-positive organisms</strong></td>
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</tr>
<tr>
<td>Methicillin-resistant Staphylococcus aureus</td>
<td>Vancomycin, imipenem-cliastatin, meropenem fusidic acid</td>
<td>Rifampicin + vancomycin, fusidic acid + glycopeptide, fosfomycin + aminoglycoside, vancomycin + floromuline</td>
<td>Imipenem + vancomycin, fusidic acid + fosfomycin, fusidic acid + glycopeptide, fusidic acid + rifampicin</td>
</tr>
<tr>
<td>Methicillin-susceptible S. aureus</td>
<td>Penicillin, cloxacin, cefazolin cephalothin</td>
<td>Penicillin + aminoglycoside</td>
<td>Fluoroquinolone + fusidic acid, fosfomycin + L-ta lactam, + fusidic acid + cloxacin</td>
</tr>
<tr>
<td>Coagulase-negative Staphylococci</td>
<td>Same indications as for MRSA, with higher resistance rates to quinolones, aminoglycosides, clindamycin, co-trimoxazole</td>
<td></td>
<td>Imipenem + fosfomycin, aminoglycoside</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>Ampicillin, imipenem, piperacillin, glycopeptide (in nosocomial UTI only)</td>
<td>Ampicillin + gentamicin, vancomycin + aminoglycoside</td>
<td>Teicoplanin + penicillin, imipenem + glycopeptides, piperacillin + teicoplanin</td>
</tr>
<tr>
<td><strong>Gram-negative organisms</strong></td>
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<tr>
<td>Escherichia coli</td>
<td>Ceftazidime/aztreonam/cefepime, amoxicillin-clavulanic acid, fluoroquinolone (in UTI)</td>
<td>Cefotaxime + amikacin, piperacillin + tazobactam, ceftoxin/aztreonam + aminoglycoside</td>
<td>Imipenem alone imipenem + aminoglycoside imipenem + fluoroquinolone</td>
</tr>
<tr>
<td>ESBL +</td>
<td>Imipenem/cefepime, fluoroquinolone (in UTI)</td>
<td>Imipenem + aminoglycoside: piperacillin + tazobactam + amikacin</td>
<td>Imipenem + ciprofloxacin</td>
</tr>
<tr>
<td>Klebsiella spp. ESBL -</td>
<td>Ceftazidime/cefoperazone/cefepime, amoxicillin-clavulanic acid</td>
<td>Piperacillin + tazobactam, ticarillin + clavulanic acid, cefotaxime + aminoglycoside</td>
<td>Imipenem alone imipenem + aminoglycoside imipenem + fluoroquinolone</td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
<td>Colistin/polyoxymycin B/subactam (high dose)</td>
<td>Meropenem/cefoperazone-subactam/ticarillin-clavulanic acid/tegcycline, cefepime + tazobactam</td>
<td>Imipenem + cefoperazone subactam / piperacillin + tazobactam/ticarillin-clavulanic acid</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>Penicillins (ticarillin, piperacillin azdacidil)</td>
<td>Ticarillon aztreonam or cephalosporins (ceftazidime, cefepime) imipenem, meropenem</td>
<td>Antipseudomonal penicillin + fluoroquinolone, aztreonam + amikacin, aminoglycoside + ciprofloxacin, fusidic acid + ciprofloxacin</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>Imipenem or meropenem cefpirome/cefepime, piperacillin + tazobactam</td>
<td>Third-generation cephalosporin + aminoglycoside, aztreonam + amikacin</td>
<td>Imipenem + fluoroquinolone, aminoglycoside + ciprofloxacin</td>
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<td><strong>Fungal sprains</strong></td>
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<td>Candida spp.</td>
<td>Amphotericin/caspofungin</td>
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<tr>
<td>Aspergillus spp.</td>
<td>Caspofungin/amphotericin</td>
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**Abbreviations:** MRSA, Methicillin-resistant Staphylococcus aureus; UTI, Urinary tract infection; ESBL, Extended-spectrum beta-lactamase

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(partially in burn patients), and surgical wounds are less often the source of bacteremia. Gram-positive organisms, MRSA and C-NS exceed Gram-negative bacilli particularly in relation to the presence of intravenous (IV) devices, central lines or peripheral IV catheters. Specific problems in antibiotic effects on Staphylococci adherent to catheters have been described. Coagulase-negative Staphylococci produce an extracellular slime matrix, in which bacteria are embedded, which interferes with the penetration of antibiotics; bacteria cannot be eliminated by traditional antimicrobial therapy. Only continued infusions of combinations of imipenem plus fosfomycin, or vancomycin or an aminoglycoside seem to offer potential efficacy. Removal of IV catheters constitutes the only therapeutic measure in most cases. Whatever the infection site as a source of bloodstream infection, the mortality rates of bacteremia range between 25% and 50%. Monitoring must take into account the organism(s) isolated from blood, the identified source of the bloodstream infection and the potential participation of sepsis signs; thus, antibiotic therapy even suitably adapted to the nosocomial pathogens involved is not sufficient. The patient’s condition requires additional measures such as antiendotoxin antibodies or newer antiendotoxin and anticytokine therapies.

**Skin and Soft-tissue Infections**

Among hospital-acquired SSTI, one selected situation particularly difficult to treat and control is that of burn wounds. Topical wound care using various agents like 0.5% AgNO₃ solution. Ten percent mafenide acetate cream, mupirocin and/or metronidazole cream and silver sulfadiazine, local antibiotics and prophylactic systemic
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**TABLE 2 | Strategies for prevention of nosocomial infections**

<table>
<thead>
<tr>
<th>General measures</th>
<th>Nosocomial pneumonia</th>
<th>Bloodstream infection</th>
<th>Surgical wound infections</th>
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<tbody>
<tr>
<td>Personnel</td>
<td>Educational programs; handwashing, gloves, gowns, etc.: control of infections at risk for healthcare workers: immunization</td>
<td>Clean or replace respiratory equipment (endotracheal tubes, suctioning devices, ventilators, etc.) between use on different patients; careful use of invasive exploratory endoscopies</td>
<td>Careful handling of catheters; aseptic techniques for insertion; search for source of bacteremia (infection focus); removal of central line when no longer required</td>
</tr>
<tr>
<td>Patient</td>
<td>Patient isolation: single room for high-risk patients; antibiotic prophylaxis; controversial, specific conditions (neutropenic, burn patients): assess daily for spontaneous respiration for early weaning from mechanical ventilation</td>
<td>Head end elevation 30–45° unless contraindicated; oropharyngeal decontamination: treatment of nosocomial sinusitis; local antibiotics (aerosols); gastric alkalization: care of enteral nutrition</td>
<td>Minimize urinary catheter use and duration of catheterization, changed at appropriate intervals; urine and blood cultures with best techniques (automated) for rapid identification of pathogens</td>
</tr>
<tr>
<td>Treatment</td>
<td>Optimal use of antibiotics, control of antibiotic use (antimicrobial use audits)</td>
<td>Surveillance of air conditioning humidity, hot water nebulizers (Legionella); isolation precautions; isolation guidelines</td>
<td>Hospital and intensive care unit surveillance (epidemiology); disposable catheters, close cooperation with microbiology</td>
</tr>
<tr>
<td>Environmental measures</td>
<td>Hospital nosocomial infection surveillance; close cooperation with microbiology; computerized systems in surveillance and fast transmission of data; proper elimination of medical waste</td>
<td></td>
<td>Sterilization and suitable disinfection measures for reusable equipment; disposable instruments whenever possible; disposal regulations</td>
</tr>
<tr>
<td>Administration (regulatory organizations, guidelines, consensus conferences)</td>
<td>Infection Control Committee: restriction policies (hospital formulary); guidelines for prevention; consensus conferences; application of guidelines</td>
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</tr>
<tr>
<td>Miscellaneous</td>
<td>Hospital design engineers for suitable structure of wards, rooms, specific isolation units and health care facilities. Close cooperation between authorities, intensivists, microbiologists, infectious diseases consultants.</td>
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</table>

**PREVENTION STRATEGIES**

Hospital-acquired infection can be prevented to a large extent by implementing three sets of precautions: (1) standard safety precautions, (2) transmission-based precautions and (3) special precautions (Table 2).22

**CONCLUSION**

Medical advances have brought lifesaving care to patients in need, yet many of these come with the risk of NI which can be devastating and fatal. As our ability to prevent NIs grows, these infections are extremely unacceptable.

Recent successes in NI elimination have been very encouraging but much more remains to be done. Improvement in hospital epidemiology surveillance, strict adherence to infection control practices, formulation of empiric antibiotic policy and implementation of guidelines for prevention of NI should result in decreasing the incidence of patient morbidity and mortality and preventing an epidemic of NI.

**REFERENCES**