REVIEW ARTICLE

Recent Advances in the Management of Nosocomial Infections

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Introduction : Nosocomial infection (NI) is defined as an infection developing in hospitalized patients, neither present nor in incubation at the time of their admission. It is associated with increased morbidity and mortality. NI is among the most difficult problems confronting clinicians who deal with severally ill patients. By prolonging the hospital stay of patients, NI adds significantly to the economic burden. The incidence of NI is estimated at 5-10% in tertiary care hospitals reaching upto 28% in ICU.

Ninety percent of the NIs are 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. Large usage of broad spectrum antibiotics in hospital environment promoted emergence of newer organisms such as Acinetobacter baumanni, S. maltophilia and B. cepacia.

The present paper deals with bacterial nosocomial pathogens (excluding mycobacterial infection) only, since they are the major causes of NI.

Eepidemiological Features of Nosocomial Infection Recent surveys on nosocomial infections have pointed out significant changes in microbial flora and their distribution in various parts of body (1-5).

Changes in Microbial Flora : The distribution of pathogens responsible for NI has changed over the years. In the early antibiotic era, hospital acquired infections were dominated by Staphylococcal infections, well controlled initially by Penicillin (6). 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 1960, resistant bacteria belonging to family enterobacteraceae (Klebsiella spp., Escherichia spp., Proteus spp.) (7), became increasingly involved in NI and in the years 1975 to 1980, the emergence of multi resistant gram negative bacilli Pseudomonas aeruginosa and Acinetobacter spp was observed, presenting difficult therapeutic problems (8-10).

More recent surveys have indicated the re-emergence of gram positive cocci including coagulase positive staphylococci, coagulase negative staphylococci and streptococci, whereas incidence of Escherichia coli and Klebsiella 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 Pseudomonas aeruginosa, Acinetobacter spp., and emergence of newer nosocomial gram negative organisms such as Burkholderia cepacia and Stenotrophomonas maltophilia (13,14).

Changes in the distribution of infection sites : Earlier studies in 1975-76 had shown urinary tract infections (UTIs) as the most common cause of NI (42%), followed by surgical wound infection (24%) and Nosocomial pneumonia (15). However a significant change in the incidence of Nosocomal pneumonia (from 17% in the early 1990s to > 30% in 1995) was observed.

With increased use of invasive procedures for therapeutic and diagnostic purposes, cancer chemotherapy, immunotherapy and advances in organ transplants, a progressive increase in the incidence of sepsis and septic shock, often related to secondary bacteremia has been observed.

Distribution of Pathogens in specific sites : In lower respiratory tract infections Pseudomonas aeruginosa and Staphylococcus aureus are the leading pathogens while in urinary tract infection Escherichia coli, Klebsiella spp., Proteus spp. And Streptococcus faecalis predominate. In bacteremia, surgical wounds and burns Staphylococci and Enterococci are leading pathogens respectively.

Management of NI : Many antimicrobial agents are available today and antibiotic therapy should theoretically

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be chosen when the infecting organism and its susceptibilities have 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.

Strategies for Management of NI : The choice of empiric antibiotic therapy for the treatment of any NI before microbiology is available requires.

i) Surveillance data on a regular basis of predominant organisms in the hospital/ICU.

ii) Surveillance of the current resistance patterns of these organisms

iii) Identification of outbreaks of NI involving one or more prevalent organisms.

Principles of Empiric Therapy : The conventional empiric therapy has to be broad enough to ensure coverage of most of the suspected pathogens. Combination therapy with an antipseudomonal penicillin (piperacillin) plus an aminoglycoside or an antipseudomonal cephalosporin (Ceftazidime) plus an aminoglycoside have been for long the initial regimen recommended officially. However, in situations suggestive of gram positive organisms such as MRSA (in institutions where this organism is endemic) the addition of a glycopeptide forms part of empiric therapy. Rifampicin, fusidic acid Streptogramins (Quinupirstin–Daltopristin) also cover most gram positive organisms.

During outbreaks of NI with high probability of cross contamination of a previously identified endemic multi resistant organism such as Pseudomonas aeruginosa, carbapenems (e.g., imipenem or meropenem) in combination with either an aminoglycoside (amikacin) or a fluoroquinolone (Ciprofloxacin) should be recommended.

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:

1. 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.
2. If Legionellosis is suspected (atypical pneumonia), erythromycin and rifampicin either alone or in combination are the antibiotics of choice[16].
3. In patients of neutropenia with neutrophil count $500/m^3$ or below and fever 38.3^oC.

Initial Antibiotic Therapy :

(i) Ceftazidime plus vancomycin. Vancomycin is given only if suspected causative agent is MRSA Penicillin resistant pneumococci or other gram positive resistant organisms.

(ii) If Vancoymycin is not required then monotherapy with Ceftazidime, Imipenem, Cefepime or meropenem is given.

(iii) If a combination is needed standard combination should be Ceftazidime plus an antipeudomonal penicillin (Like Piperacillin) (17,18).

Therapeutic Strategies of Documented NI : The identification of the aetiological agents involved in a given outbreak of NI should rely on an efficient clinical microbiology laboratory and good epidemiology practices within the hospital wards. Moreover the choice of single agent or a combination based on clinical consideration should also refer to the known patterns of susceptibility/resistance (19).

The patient's condition, severity of underlying disease, the presence of various devices (Catheters, ventilatory equipment, prosthesis etc.) are important factors which may interfere with the choice of a single agent or of 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 (eg. CSF) and variable penetration of drugs into cells (macrophages) to reach and kill intracellular organisms (legionella pneumophilia).

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

Gram Negative Organisms

Monotherapy

Although less frequently used than combination therapy, monotherapy has been recommended using a third or fourth generation cephalosporins, aztreonam or carbapenems.

With broad spectrum cephalosporins depression of class I cephalosporinase has been observed. The potential improvement of new cephalosporins, Cefpiromes/ Cefepime have been attributed to the return to antistaphylococcal activity as compared with Cefotaxime/ Ceftazidime and a rapid intrabacterial penetration resulting from zwitterionic character of these drugs.

Other options are a b-lactam plus a b-lactamase inhibitor such as amoxicillin + clavulanate (co-amoxyclav) or piperacillin + tazobactum or cefoperazone + sulbactum etc

Combination therapy

Besides conventional combination of a b.lactam plus aminoglycoside which offers broad spectrum of antibacterial activity, the association of Ciprofloxacin with Ceftazidime in P. aeruginosa NI, has shown efficacy and prevention of emergence of resistance during therapy. It has been confirmed that quinolones combined with a B-lactam (Ureidopenicillin, Ceftazidime or Imipenem) reduce the risk of emergence of resistance in S. pneumoniae, Seroratia marcescens, E. cloacae and P. aeruginosa.

Gram Positive Organisms

Multi-resistant Gram positive organisms pose specific problems such as Methicillin resistant Staphylococci aureus that are also resistant to rifampicin, aminoglycosides and fluoroquinolones. The current drugs of choice for the treatment of MRSA infections are Vancomycin, teicoplanin and linezolide.

Promising activities of a new streptogramins (quinupristin-dalfopristin) have been established in Staphylococci and E. faecium which were resistant to Vancomycin, Imipenem, Gentamicin and Ciprofloxacin.

Antibiotic Therapy in selected Nosocomial Infections

Nosocomial pneumonia

Pneumonia is the second most common nosocomial infection and is associated with substantial morbidity and mortality. The common causative agents are P.aeruginosa, K.pneumoniae, S.pneumoniae, H.influenzae, E.coli, M.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 2 major pathogenic organisms, Pseudomonas aeruginosa and S.aureus impose the use of combination of synergistic antibiotics – b.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 B.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 concentrations upto 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 super infection in cystic fibrosis patients may require achievement of higher tissue concentrations.

Bacteraemia: Nosocomial blood stream infection

There are several sources of bacteraemic extension, mainly nosocomial pneumonia and UTI. Other foci of infection such as skin and soft tissue infections (particularly in burn patients), and surgical wounds are less often the source of bacteraemia. Gram positive organisms, MRSA and C-NS exceed gram negative bacilli particularly in relation to the presence of IV devices, central lines or peripheral IV catheters. Specific problems in antibiotic effects on Staphylococci adherent to catheters have been described (20). C-NS (coagulase negative staphylococci) produce an extra cellular slime matrix in which bacteria are embedded and which interferes with the penetration of antibiotics: Bacteria cannot be eliminated by traditional antimicrobial therapy. Only continues 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 blood-stream infection, the mortality rates of bacteraemia range between 25-50% (21). Monitoring must take into account the organism(s) isolated from blood, the identified source of the blood stream 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 (SSTI)

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% $AgNO_3$ solution, 10.0% mafenide acetate cream and silver sulfadiazine, local antibiotics and prophylactic systemic antibiotic therapy constitute the best approach to prevent burn wound infection. Systemic antibiotics therapy although controversial, is recommended for prevention of infection immediately after burn injury when host defences are reduced.

Paediatric NI

These are different from NIs of adults. The predominant sites are digestive tract, respiratory tract and blood stream. The predominant nosocomial pathogens are gram positive organisms and there is a high risk of bacteraemia with secondary infections (meningitis, bone and joint infections etc.). Management of NI in children is particularly difficult because of problems in collecting the appropriate specimens for microbiology diagnosis and as a result in designing suitable therapeutic strategies (22).

Table I. Therapeutic strategies for Documented Nosocomial Infections (24, 25, 26)

	Monotherapy	Conventional combinations	Alternatives
Gram-negative organisms			
Escherichia coli	Ceftazidime or aztreonam or cefpirome/cefepime: amoxicillin-clavulanic acid: fluoroquinolone (in UTI)	Cefotaxime + amikacin: piperacillin + tazobactam: ***cefoxitin or aztreonam +*** aminoglycoside	Imipenem alone Imipenem + aminoglycoside imipenem + ***fluoroquinolone***
Klebsiella spp: SBL -	Ceftazidime or : cefoperazone or cefepime/cefpirome amoxicillin-clavulanic acid	Piperacillin + tazobactam: ticarcillin + clavulanic acid: cefotaxime + aminoglycoside	Imipenem alone Imipenem + aminoglycoside : imipenem + fluoroquinolone
ESBL+	Imipenem or cefepime: fluroquinolone (in UT)	Imipenem + aminoglycoside: piperacillin + tazobactam + amikacin	Imipenem + ciprofloxacin
Enterobacter spp.	Imipenem or meropenem: cefpirome/cefepime: piperacillin + tazobactam	Third generation cephalosporin + aminoglycoside: aztreonam + amikacin	Imipenem + fluoroqulnolone: aminoglycoside + ciprofloxacin
Pseudomonas aeruginosa	Penicillins (ticarcillin, piperacillin, azlocillin). Cephalosporins (ceftazidime, cefpirome/cefepime) Imlpenem, meropenem	Ticarcillin aztreonam or ceftazidime + sulbactam + tobramycin or amikacin: ceftazidime + fluoroquinolone	Antipseudomonal penicillin + fluoroquinolone: aztreonam + amikacin: aminoglycoside + ciprofloxacin: fosfomycin + ciprofloxacin
Gram-Positive organisms			
Staphylococcus aureus: MSSA (methicillin-susceptible)	Penicillins, cloxacillin: cefazolin cefalothin: Second generation cephalosporin: cefotaxime aminoglycosides	Penicillin + aminoglycoside (oxacillin + gentamicin): tetracycline + aminoglycoside: amoxicillin + clavulanic acid: ampicillin + sulbactam	Fluoroquinolone + fusidic acid: fosfomycin + L-lactam: + fusidic acid + cloxacillin
MRSA (methicillin-resistant)	Vancomycin: imipenem-cilastatin: meropenem: fusidic acid	Rifampicin + vancomycin: fusidic acid + glycopeptide: fosfomycin + aminoglycoside: vancomycin + fluoroquinolone	Imipenem + vancomycin: fusidic acid + fosfomycin: fusidic acid + glycopeptide: fusidic acid + rifampicin:
Coagulase-negative staphylococci	Same indications as for MRSA, with higher resistance rates to : quinolones, aminoglycosides, clindamycin, cotrimoxazole.		Imipenem + fosfomycin: aminoglycoside
Enterococcus spp.	Ampicillin: imipenem: piperacillin: glycopeptide (in nosocomial UTI only)	Ampicillin + gentamicin: vancomycin + aminoglycoside	Teicoplanin + penicillin: imipenem + glycopeptides: piperacillin + teicoplanin

Table II. Strategies for Prevention of Nosocomial Infections (24, 25, 26)

	General measures	Nosocomial pneumonia	Bloodstream infection	Surgical wound infections
Personnel	Educational programmes: hand-washing, gloves, gowns, etc.: control of infections at risk for healthcare workers: Immunisation	Maintenance, disinfection of respiratory equipment (endotracheal tubes, suctioning devices, ventilators, etc): careful use of invasive exploratory endoscopies	Careful manipulation of catheters: aseptic technique for insertion; search for source of bacteraemia (infection focil)	Preparation of operative team (surgical gloves, gowns, masks, etc.)
Patient	Patient isolation: single room for high risk patients: antibiotic prophylaxis: controversial, specific conditions (neutropenic, burn patients): SDD: controversial, topical treatments for colonised sites	Oropharyngeal decontamination: treatment of nosocomial sinusitis: local antibiotics (aerosols): gastric alkalinisation: semi-recumbent position: care of enteral nutrition	Duration of catheterisation, changed at appropriate intervals : adjusting for severity of underlying disease: blood cultures with best techniques (automated) for rapid identification of pathogens: SDD limits translocation and endotoxin release	Wound classification (clean, clean-contaminated, dirty): minimise preoperation stay: suitable skin preparation, hair removal: antibiotic prophylaxis
Treatment	Optimal use of antibiotics, control of antibiotic use (antimicrobial use audits)			
Environmental measures	Hospital noscomial infection surveillance: close cooperation with microbiology: computerised systems in surveillance and fast transmission of data: proper elimination of medical waste	Surveillance of air conditioning humidities, hot water nebulisers (Legionella): isolation precautions: isolation guidelines	Hospital and intensive care unit surveillance (epidemiology): disposable catheters, close cooperation with microbiology	Limiting source of exogenous contamination: excellent surgical technique, limiting "dead space" exposing wound: proper wound dressing
Administration (regulatory organisations, guidelines, consensus conferences)	Infection Control Committee: restriction policies (hospital formulary) : guidelines for prevention: consensus conferences: application of guidelines			Sterilization and suitable disinfection measures for reusable equipment: disposable instruments whenever possible: disposal regulations
Miscellaneous	Hospital design engineers for suitable structure of wards, rooms, specifc isolation units and health care facilities. Close cooperation between authorities, microbiologists, infections diseases consultants.			

Strategies for Prevention of Nosocomial Infections

Prevention plays a major role in the control of NI. Numerous guidelines have been established in US and European Union. Hospital infection control committees are increasingly organized in modern hospitals to advice regarding the control and prevention of NI.

Many preventive measures have been recommended. These include isolation policies, administrative measures and hospital epidemiology surveillance. These measures are applied to reduce morbidity, length of hospital stay, mortality and hospital costs. Among the published guidelines three main approaches are as follows :

1. Elimination of Endogenous nosocomial pathogens to reduce oropharyngeal, intestinal and skin colonization.
2. Use of methods to prevent cross contamination and to control various sources of nosocomial pathogens that can be transmitted from patient to patient or from personnel to patient i.e. proper disinfection and care of catheters, respiratory equipments, humidifiers, endotracheal tube and dialysis systems.
3. Use of antibiotic prophylaxis in post operative and high risk patients (burn patients, patients in ICUs etc.). Aerosolized polymyxin-B and/or endotracheal aminoglycosides can be given to prevent Pseudomonas and/or Acinetobacter pneumonia which have the highest mortality rates.

Specific immuno prophylaxis has been recommended in high risk situations against Pseudomonas and

Klebsiella infections. In addition selective digestive decontamination (SDD) has been advocated in ICU patients (23). The use of SDD should prevent colonization of the oropharynx and gut by potentially pathogenic bacteria, as the digestive tract is important reservoir for multiresistant organisms particularly gram negative bacilli and thus the source of a variety of NIs. Topical chemoprophylaxis includes nonabsorbable antibiotics e.g. Neomycin etc.

Conclusion

Improvement in hospital epidemiology surveillance, infection control practices and applications of guidelines for prevention of NI should result in decreasing incidence of morbidity and mortality. However, NI still remains a major threat in high risk patients.

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