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NOSOCOMIAL INFECTIONS: A REVIEW

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INTRODUCTION

Health-care-associated infection (HAI) is a major global safety concern for both patients and health-care professionals. HAI is defined as an infection occurring in a patient during the process of care in a hospital or other health-care facility that was not manifest or incubating at the time of admission. This includes infections acquired in the hospital and any other setting where patients receive health care and may appear even after discharge.[1,2]

Patients in the intensive care unit (ICU) are at risk for dying not only from their critical illness but also from secondary processes such as nosocomial infection. Nosocomial infections occur world-wide, incidence is 5-10% in tertiary care hospitals reaching upto28% in ICU and affect both developed and resource-limited countries.[3] Populations at stake are patients in Intensive Care Units (ICUs), burn units, undergoing organ transplant and neonates. According to Extended Prevalence of Infection in Intensive Care (EPIC II) study, the proportion of infected patients within the ICU are often as high as 51%.[4] Reports from ICU settings consistently show a high burden of device-associated nosocomial infections.[5,6]

Nosocomial infections are caused by a wide range of pathogens, invasive devices such as catheters and ventilators employed in modern health care are associated to these infections. Ventilator-associated pneumonia and central line infections are common sites of infections and are associated with high mortality.[7]

Hospital acquired infections not only add to functional disability and emotional stress of the patient but in some cases, also lead to disabling conditions that reduce the quality of life and may lead to death. With increasing infections, there is an increase in prolonged hospital stay, increased antimicrobial resistance, increase in socio-economic disturbance, and increased mortality rate.

Hospital Acquired Infection causing organisms are:
Nosocomial pathogens include bacteria, viruses and fungal parasites. Bacteria likeEnterobacter faecium, Staphylococcus, strep. Viridians, Klebsiella, Acinetobacter, Pseudomonas aeruginosa, Proteus, Enterococcus, E.coli, Cl.difficile. Virus likeHBV, HCV, CMV, rubella, varicella, SARS, Rota virus and fungal parasites candida, Aspergillus.

Types of nosocomial infections
These infections include central line-associated bloodstream infections (CLABSI), catheter-associated urinary tract infections (CAUTI), surgical site infections (SSI), Hospital-acquired Pneumonia (HAP), Ventilator-associated Pneumonia (VAP), and Cl. difficile infections (CDI). Symptoms that favour an infection include productive cough, shortness of breath, abdominal pain, rebound tenderness, altered mental status, palpitations, suprapubic pain, polyuria, dysuria, and costovertebral angle tenderness.

Appropriate antimicrobial use: The selection of antimicrobials should be based upon the patient's tolerance, nature of disease and pathogen. The aim is to use a drug that is selectively active against most likely pathogen and least likely to cause resistance and adverse effects.[8] Antimicrobial prophylaxis should be used when it is appropriate, to reduce postoperative incidence of surgical site infections.[9,10]

Self medication with antibiotics, incorrect dosage, prolonged use and lack of standards for healthcare workers are the main factors responsible for increase in resistance. This resistance threatens the effective control against bacteria that causes UTI, pneumonia and bloodstream infections. Highly resistant bacteria such as MRSA or multidrug-resistant Gram-negative bacteria are the cause of high incidence rates of nosocomial infections worldwide.[11]

1. Central line-associated bloodstream infections (CLABSI)

A central line-associated bloodstream infection (CLABSI) is defined as a laboratory-confirmed bloodstream infection not related to an infection at another site that develops within 48 hours of central line placement. CLABSIs are deadly nosocomial

infections with the death incidence rate of 12%–25%.[12] The presence of bacteraemia initiated by the intravenous catheter is the hallmark of catheter-related bloodstream infection (BSI). Prolonged use of central venous catheters can cause serious bloodstream infections resulting in compromised health and increase in care cost.[13] Common organisms for CLABSI are candida spp, Enterobacteriaceae, and staph aureus.[14] When CLABSI is suspected, empirical treatment should be instituted promptly. In general, coverage for common gram-positive and gram-negative organisms is necessary.

1. Parenteral vancomycin, if MRSA is prevalent. Otherwise, parenteral anti-staphylococcal penicillin or cephalosporins such as nafcillinor cefazolin would be given. In the case of vancomycin-resistant enterococci (VRE), daptomycin is the drug of choice.

2. The antibiotic choice for gram-negative coverage should be based on the risk of pseudomonal infection. If the risk of Pseudomonas is low, then a third-generation cephalosporin such as ceftriaxone is appropriate. In patients with a critical illness or high risk for resistant organisms, a combination of a beta-lactam (lactamase inhibitor) and an aminoglycoside is preferred - Cefepime or carbapenem with or without an aminoglycoside. Agents against *Pseudomonas aeruginosa* such as 3rd and 4th generation cephalosporins like Cefoperazone, ceftazidime, cefepime, carbapenems like imipenem, meropenemare required in severe illness.

3. Echinocandins (micafungin, caspofungin, anidulafungin) are preferred agents for suspected candidemia if azole resistance is suspected, otherwise, intravenous fluconazole would be sufficient.

Only for long-term catheters, salvage (systemic therapy coupled with antimicrobial lock [heparin + high concentration of antimicrobial agent that is selected based on susceptibility results]) can be attempted in limited instances such as:- Uncomplicated CLABSI caused by organisms other than *Staph. aureus*, *Pseudomonas aeruginosa*, Bacillus spp, Micrococcus spp., Propionibacteria, fungi,ormycobacteria.[15]

2. Catheter associated urinary tract infections (CAUTI): CAUTI is the most usual type of nosocomial infection globally. CAUTIs are caused by endogenous native microfloraof the patients. Catheters placed inside serves as a conduit for entry of bacteria whereas the imperfect drainage from catheter retains some volume of urine in the bladder providing stability to bacterial residence.[16,17] Common pathogens that are known to cause CAUTI are Enterococcus, staphylococcus aureus, Pseudomonas, proteus, Klebsiella, and Candida. Some organisms, such as *Pseudomonas* species and Proteus species, can form tough biofilms around catheters. Sometimes, these pathogens produce enzymes that inactivate the antimicrobial agents, making it harder to treat these infections.[18,19]

When suspecting catheter-associated urinary tract infections, the old catheter must be removed, and a urine sample from the newly placed catheter must be obtained, preferably before initiating antibiotics. For catheter-associated UTIs, seven days of antibiotics are typically recommended. However, in case of a delayed response or bacteremia, the antibiotic course could be extended to 10 - 14 days.[20]

Recommended Antibiotics:[21]

Antibiotic	**Dosage and course length**
First-choice oral antibiotic if no upper UTI symptoms:	
Nitrofurantoin- if eGFR ≥45 ml/minute	100 mg modified-release twice a day for 7 days
Trimethoprim–if a low risk of resistance	200 mg twice a day for 7 days
Amoxicillin (only if culture results available and susceptible)	500 mg three times a day for 7 days
Second-choice oral antibiotic if no upper UTI symptoms (when first-choice not suitable)	
Pivmecillinam (a penicillin)	400 mg initial dose, then 200 mg three times a day for a total of 7 days
First-choice oral antibiotic if upper UTI symptoms:	
Cefalexin	500 mg twice or three times a day (up to 1 to 1.5 g three or four times a day for severe infections) for 7 to 10 days
Co-amoxiclav (only if culture results available and susceptible)	500/125 mg three times a day for 7 to 10 days
Trimethoprim (only if culture results available and susceptible)	200 mg twice a day for 14 days
Ciprofloxacin (consider safety issues)	500 mg twice a day for 7 days
First-choice intravenous antibiotic (if vomiting, unable to take oral antibiotics or severely unwell). Antibiotics may be combined if susceptibility or sepsis a concern	
Co-amoxiclav (only in combination, unless culture results confirm susceptibility)	1.2 g three times daily
Cefuroxime	750 mg to 1.5 g three or four times a day
Ceftriaxone	1 - 2 g once a day
Ciprofloxacin (consider safety issues)	400 mg twice or three times a day

Gentamicin	Initially 5 to 7 mg/kg once a day, subsequent doses adjusted according to serum gentamicin concentration
Amikacin	Initially 15 mg/kg once a day (maximum per dose 1.5 g once a day), subsequent doses adjusted according to serum amikacin concentration (maximum 15 g per course)
Second-choice intravenous antibiotic	

Antibiotics for pregnant women:[21]

Antibiotic	Dosage and course length
First-choice oral antibiotic:	
Cefalexin	500 mg twice or three times a day (up to 1 to 1.5 g three or four times a day for severe infections) for 7 to 10 days
First-choice intravenous antibiotic (if vomiting, unable to take oral antibiotics or severely unwell).	
Cefuroxime	750 mg to 1.5 g three or four times a day
Second-choice intravenous antibiotic or combining antibiotics if susceptibility or sepsis a concern:	

3. Surgical site infections (SSI): SSIs are nosocomial infections be fall in 2%–5% of patients subjected to surgery. These are the second most common type of nosocomial infections mainly caused by Staphylococcus aureus resulting in prolonged hospitalization and risk of death.[22] The pathogens causing SSI arise from endogenous microflora of the patient. Theincidence may be as high as 20% depending upon procedure and surveillance criteriaused.[23] Common causative organisms for SSI include staph aureus, coagulase-negative staphylococcus, Enterococcus, E Coli, Pseudomonas aeruginosa, Enterobacter, Klebsiella pneumonia and sometimes include Methicillin-resistant staphylococcus aureus (MRSA).[24]

Not all SSIs require antibiotic treatment: minor infections may respond to drainage of pus and topical antisepsis.First-line antibiotic therapy i.e. empirical therapy should be broad-spectrum. SSIs after clean-contaminated surgeryshould be treated with an empirical antibioticregimen that includes activity againstanaerobic bacteria (for eg., metronidazole, co-amoxiclav, piperacillin-tazobactam ormeropenem). SSIs inpatients of MRSA carriageshould be treated with an empiricalantibiotic regimen that includes activity against of MRSA (for eg.,Vancomycin,Daptomycin, Linezolid, Clindamycin, Tigecycline, Ceftaroline).[25]

Recommended parenteral antibiotic therapies for wound infections[26]	
Skin and Soft Tissue Infections	Suggested antimicrobial Therapies
Superficial SSI (wound infections)	Cefazolin, 1-2 g IV q 6h
	Ceftriaxone, 1-2 g IV q 24h
	Cefoxitin, 2 g IV q 6h
	Ampicillin / Sulbactam, 3 g IV q 6h
	Piperacillin / Tazobactam, 3.375 g IV q 6h
Deep/ Organ SSI	Clindamycin, 900 mg IV q 8h, and Gentamicin, 5mg/kg IV q 24h or 1.5 -2 mg/kg IV q 8h Ceftriaxone, 2 g IV q 24h and Clindamycin, 900 mg IV q 8h Ampicillin, 2 g IV q 4h, and gentamicin, 5mg/kg IV q 24h or 1.5- 2 mg/kg IV q 8h

4. Ventilator associated pneumonia (VAP): Pneumonia is the second most common nosocomial infection in critically ill patients, affecting 27% of all critically ill patients[27] Eighty-six percent of nosocomial pneumonias are associated with mechanical ventilation and are termed ventilator-associated pneumonia (VAP). It usually occurs within 48 h after tracheal incubation.The most common pathogens for VAP are staph aureus and pseudomonas aeruginosa.[28]

Empirical therapy includes ceftriaxone, quinolones (levofloxacin, moxifloxacin, or ciprofloxacin), ampicillin/sulbactam, or ertapenem. In multidrug-resistant organisms, the empirical therapy is broadened to include (i) either an antipseudomonal cephalosporin (cefepime or ceftazidime), an antipseudomonalcarbepenem (imipenem or meropenem), or a β-lactam/β-lactamase inhibitor (pipercacillin-tazobactam) plus (ii) an antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or an aminoglycoside (amikacin, gentamicin, or tobramycin) plus linezolid or vancomycin.[29,30] IVcolistin therapy forMDR *Acinetobacterc*spp. and *Pseudomonas* spp. Tigecycline against carbapenem-resistant *Acinetobacter* spp.[31] A minimum of 7–10 days treatment is recommended. However, in MDR cases antibiotic course could be extended to 14 -21 days.[32]

5. Hospital-acquired Pneumonia (HAP): Hospital-acquired pneumonia (HAP) is a common infection in

hospitals, which is the second most common nosocomial infection.Intubated patients may have rates of pneumonia 7 to 21- fold higher than patients without a respiratory therapy device.[33] HAP is usually found in patients who have been in the ICU for at least 48 hours.The most common pathogens for HAP are staph aureus, pseudomonas aeruginosa, E Coli and Klebsiella pneumonia.[34]

Not at High Risk of Mortality and no Factors Increasing the Likelihood of MRSA:[35]
One of the following:
Piperacillin-tazobactam or Cefepime or Levofloxacin or Imipenem /Meropenem

Not at High Risk of Mortality but With Factors Increasing the Likelihood of MRSA:[35]
One of the following:
Piperacillin-tazobactam or Cefepime /ceftazidime or Levofloxacin/ Ciprofloxacin or Imipenem/Meropenem or Aztreonam Plus Vancomycin or Linezolid.

High Risk of Mortality:[36]
Two of the following, avoid 2 β-lactams:
Piperacillin-tazobactam or Cefepime /ceftazidime or Levofloxacin / Ciprofloxacin or Imipenem/ Meropenem or Amikacin/ Gentamicin Tobramycin or Aztreonam Plus Vancomycin or Linezolid.

For MSSA:[37]
Piperacillin-tazobactam, cefepime, levofloxacin, imipenem, meropenem. Oxacillin, nafcillin, and cefazolin are preferred for the treatment of proven MSSA
If patient allergic to penicillin useaztreonam

First episode of the infection	**Antibiotics**
Non-severe disease	• Vancomycin 125 mg orally four times a day for 10 daysOR • Fidaxomicin 200 mg orally twice a day for 10 days • If above agents are unavailable: metronidazole 500 mg orally three times a day for 10 days
Severe disease	• Vancomycin 125 mg orally four times a day for 10 daysOR • Fidaxomicin 200 mg orally twice a day for 10 days
Fulminant disease (previously referred as severe complicated)	• Vancomycin 500 mg orally or via nasogastric tube four times a dayAND • Metronidazole 500 mg IV 3 times a day + alternatively If ileus is present: vancomycin per rectum (vancomycin 500 mg in 100 ml saline as enema) four times a day (10–14 days)
First recurrence	If the first episode was treated with metronidazole or fidaxomicin: • Vancomycin 125 mg orally four times a day for 10 days If the first episode was treated with vancomycin: • Vancomycin pulsed-tapered orally (each dose 125 mg): Four times daily for 10–14 days and then twice a day for 7 days than once a day for 7 days, than every 2 or 3 days for 2-8 weeks OR Fidaxomicin 200mg orally twice a day for 10 days Second of Subsequent recurrences: • Vancomycin pulsed-tapered orally (regimen as above) OR • Fidaxomicin 200mg orally twice a day for 10 days OR • Vancomycin 125mg orally four times a day for 10 days, followed by rifaximin 400 mg three times daily for 20 days OR • Faecal microbiota transplantation

Antibiotics recommended:[44]

6. Clostridium difficile infections (CDI): *Clostridium difficile* (*C. difficile*) is a Gram-positive, anaerobic bacillus, which is widely distributed in the intestinal tract of humans. The frequency and severity of *C. difficile* infection has been increasing worldwide to become one of the most common hospital-acquired infections.[38] A length of stay > 2 weeks has been shown to be a risk factor for CDI.[39]Which includes: immune status, comorbidities, hospitalizations, long-term care facilities, and factors that disrupt normal colonic microbiome (antibiotics, other medications, surgery).[40] Antibiotics of choice are vancomycin, fidaxomicin, and metronidazole, though metronidazole is

considered as inferior.Fecalmicrobiota transplantation (FMT) is reserved for severe refractory cases.[41]FMT has been considered as an alternative therapy to treat resistant CDI. It involves infusing intestinal microorganisms (in a suspension of healthy donor stool) into the intestine of patients to restore the intestinal microbiota. The rationale of FMT is that disruption of the normal balance of colonic flora allows C. difficile strains to grow and produce CDI. By reintroducing normal flora via donor feces, the imbalance may be corrected, and normal bowel function re-established.[42] FMT has not been widely adopted as a therapeutic tool probably due to concerns regarding safety and acceptability.[43]

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