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REVIEW

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Nosocomial infections in neonatal intensive care units: cost-effective control strategies in resource-limited countries.

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Abstract *Background:* Nosocomial infections or hospital-acquired infections constitute a global health problem. They lead to significant morbidity and mortality in both developed and resource-limited countries. The neonatal intensive care unit (NICU) is a suitable environment for disseminating these infections; underscoring the need for preventive intervention measures.
Objectives: This review aims to highlight the global burden of nosocomial infections in neonatal intensive care units (NICUs), to discuss their epidemiology and clinical spectrum, as well as the cost-effective control strategies in resource-limited settings.
Sources: Sources of information were from Google searches and PubMed- linked articles using the key words- nosocomial infections, neonatal intensive care unit, control. Related articles from hard copies of medical literature and journals were also gathered.
Results: Although paucity of data exists on the incidence of nosocomial infections in NICUs in developing countries, reports from developed countries indicate a range of 6% to 25%. Much higher figures were noted in some developing countries. Several risk factors for nosocomial infections were identified but varied in different NICUs surveyed. Effective control strategies have been recommended but hand washing or hand hygiene appears universally applicable in both developed and resource-limited countries. Economic analyses of these strategies in developed countries have established their cost-effectiveness while the adaptability of hand hygiene program to resource-limited settings has been demonstrated in a World Health Organization pilot study in sub-Saharan Africa.
Conclusion: Hand washing or hand hygiene by health-care personnel remains the most important evidence-based and cost-effective control strategy for the spread of nosocomial infections in NICUs in resource-limited countries.

Key words: nosocomial infections; neonatal intensive care unit;control.

Introduction

Nosocomial infections or hospital-acquired infections constitute a global health problem,[1] and contribute to significant morbidity and mortality, longer duration of hospitalization, as well as increased cost of treatment in both developed and resource-poor countries.[2]

For instance in the United States, statistics show that nosocomial infections occur in 5% of all acute care hospitalizations with more than 2 million patients affected annually resulting in an added expenditure in excess of $4.5billion,[2,3]while in the United Kingdom, an audit report noted that 1 in 11 patients were affected with a mortality rate of 13% and a prolongation of hospital stay by a factor of 2.5.[4] Within the tropics-especially the sub-Saharan Africa- the picture may not be different despite scant documentation. Nevertheless, nosocomial infections remain a major cause of preventable morbidity and mortality in developing countries where infection rates are relatively higher due to poor infection control practices, lack of supervision and inappropriate use of limited resources and overcrowding of hospitals.[5]

The newborn infants in neonatal intensive care units (NICUs) form a vulnerable group for these infections due to their sudden transition to an environment totally different from the sterile intra-uterine environment. Their immature immune system, exposure to invasive procedures and devices, frequent contacts by health-care

personnel and the frequent use of antibiotics in their treatment protocol are additional risk factors.[6]
This review aims to highlight the global burden of these infections in NICUs, to discuss their epidemiology and clinical spectrum, as well as the cost-effective control strategies in resource-limited countries.

Definition of nosocomial infection

Nosocomial infection has been defined by the US Department of Health and Human Services for Disease Control and Prevention as an infection occurring during hospitalization which was not present or incubating at the time of admission.[7]The organisms causing most nosocomial infections usually emanate from the patient's own body (endogenous flora), or from contact with hospital staff, contaminated devices and consumables (cross-contamination), and from the hospital environment (exogenous flora).[5] The risk factors have therefore been categorized as *iatrogenic risk factors* which include invasive procedures and antibiotic use or prophylaxis(indwelling vascular lines and catheters); *organizational risk factors* comprising contaminated water systems, staffing and physical layout of the health facility(nurse-to-patient ratio, open beds close together);and *patient risk factors* which consist of the severity of illness, the underlying immune-compromised state and length of hospital stay.[8]

The global trend in incidence of nosocomial infections in NICUs

The nosocomial infection rate in NICUs has increased over the past several years;[9]most reports from the Western world[10-14] indicate that the incidence ranges from 6% to 25% with a significant variation by birth weight of the babies and treatment condition. A study by the European Study Group for instance found an infection rate of 7% in seven NICUs,[15]while some workers in Poland reported a higher incidence of 38.5%.[16] In the Middle East, an incidence of 13.7 infections per1000 patient-days was recorded in a hospital in Saudi Arabia.[17]Elsewhere in Far East Asia, an incidence of 25.3% was observed by other investigators in Japan.[18]

In developing countries, especially in Africa, paucity of data exists on the incidence of neonatal nosocomial infections even though several factors promote the high incidence rates of these infections generally reported in these regions. However in Brazil, an infection rate of 51% has been documented among all NICU admissions;[19] the variability in infection rates has been attributed to gestational age, distribution of neonates surveyed for the report, and the specific environment and care practices.[20] These statistical data clearly indicate a disparity in the global picture of these infections as the burden appears to weigh more in resource-limited countries than in developed countries.

Epidemiology and clinical spectrum

The major challenge in the control of nosocomial infections is the development and spread of antibiotic-resistant bacteria as intensive care units have become an important breeding ground;[21] following exposure to heavy antibiotic use, a high density patient population in frequent contact with healthcare staff, as well as the attendant risk of cross-infection.[22, 23]

The incidence of neonatal nosocomial infections managed in NICU is inversely proportional to gestational age and birth weight. In neonates with birth weight less than 1.5kg, it ranges from 5 to 32%; in those weighing less than 1kg, it rises to 40% and up to 46% in babies born before the third trimester.[24] In fact, among several risk factors identified for these infections in NICUs, birth weight appears to be the most important risk factor.[25]This observation is supported by several studies which indicate that the risk of nosocomial infection increases with reduction in birth weight.[10-14]

However, a comparison of the findings of some researchers- who conducted logistic regression analysis of identified risk factors associated with nosocomial infections in NICUs- show obvious differences. Workers in Saudi Arabia[17] reported mechanical ventilation and total parenteral nutrition as significant risk factors while gender, birth weight, method of delivery, gestational age and intravenous lines were not observed as predisposing factors. Conversely, some Japanese authors[18] demonstrated that gender, birth weight and insertion of a central venous catheter were significant risk factors while artificial ventilation, umbilical artery catheter, umbilical venous catheter and urinary catheter were not noted as risk factors. The reason for this discordance in their findings is not clear but may well be due to peculiarities of the environment studied and the care practices.

Notably, it has been established that premature and very-low-birth-weight infants appear to be particularly susceptible to nosocomial infections due to their relative immune deficiency such as poor phagocytosis and hypogammaglobinaemia.[26]Male gender is also associated with an increased risk.[27]
Clinical practice-related or iatrogenic risk factors include empirical or previous antibiotic use,[28] particularly exposure to broad-spectrum antibiotics like 3rd generation cephalosporin,[29] the need for mechanical ventilation, [30] exposure to a central venous catheter, [31] catheter hub manipulation and colonization, [32] as well as prolonged exposure to total parenteral nutrition and/or intravenous lipids,[33]especially in nosocomial fungal sepsis.

Regarding environmental factors, evolution of concepts has occurred over decades. In the 1970s, most NICUs maintained near-operating-room conditions based on the concept that the greatest risk for nosocomial infection is exogenous.[34] In the 1980s, recognition that most infections are endogenous culminated in relaxation of parental visiting restrictions. It was in the 1990s that lack of space was recognized as fostering nosocomial infections.[35]
Currently, justified concerns remain about infection finding its way into the NICU from the community, as

well as major concerns for cross-contamination such as methicillin-resistant Staphylococcus aureus (MRSA) and colonizing organisms becoming invasive (Staphylococcus epidermidis, candida) especially among very premature and extremely low birth weight babies.[34]
Approximately 85% of all NICU surfaces will grow nosocomial pathogens with over 50% contaminated by two or more pathogenic organisms; [35] the reservoirs for transmission have been reported and include soap bottles and sinks, [36] resuscitators, [37] suction equipment, [38] latex gloves, [39] hands, [40] and several others. In many developing countries, the rates of nosocomial infections are markedly higher as a result of these environment-related factors.

Several studies indicate that pneumonia and primary blood stream infections are the most common nosocomial infections in NICUs, [16, 17, 41] while at the other end of the clinical spectrum are the less frequent infections involving the skin and soft tissues, the urinary tract and the central nervous system. Blood stream infections (BSI) or nosocomial sepsis may also accompany pneumonia, urinary tract infection and meningitis. The clinical features of nosocomial sepsis are non-specific and include increasing apnoea, feeding intolerance, abdominal distension, or guaiac-positive stools, lethargy, need for increased respiratory support and hypotonia.[27] The most common laboratory indicators are abnormal white blood cell count, unexplained metabolic acidosis and hyperglycaemia.[42] However, the absence of good predictors for nosocomial sepsis is indeed one of the causes for antibiotic overuse in NICUs.[42]

Common pathogenic isolates causing nosocomial infections

A historical perspective of the epidemiology of pathogens responsible for neonatal nosocomial infections shows a dramatic change over decades.[24] During the 1950s, staphylococcus aureus phage type 80/81 was the most common nosocomial pathogen in hospitalized infants. During the 1960s, the picture changed to gram-negative bacilli especially Pseudomonas aeruginosa, Klebsiella species and Escherichia coli. A decade later, coagulase-negative staphylococcus (predominantly staphylococcus epidermidis) and staphylococcus aureus including methicillin-resistant staphylococcus aureus (MRSA) evolved as the predominant isolates in the NICU; [24] in contemporary times, gram-positive cocci continue to cause significant proportion of infections and many causative pathogens such as MRSA, coagulase-negative staphylococcus (CoNS) and vancomycin-resistant enterococci (VRE) have become multi-drug resistant. Gram-negative bacilli are however causative pathogens in about 20% to 30% of nosocomial sepsis and 30% of nosocomial pneumonia.[16, 17]

Generally, the most common pathogen implicated in nosocomial neonatal sepsis in developed countries is reported to be coagulase-negative staphylococci; [43] the scenario remains different in developing countries where gram-negative pathogens are predominant.[44]

For instance, a study in Turkey[45] shows that the most common causative organisms isolated in their order of frequency in a NICU were gram-negative bacteria (klebsiella species, pseudomonas species.), gram-positive bacteria (coagulase-negative staphylococci), and candida species. Elsewhere in India, about 72% of bacterial isolates reported in a NICU were gram-negative bacilli; comprising klebsiella species, pseudomonas species, Escherichia coli, Enterobacter species, Actinobacter species, citrobacter species and other non-fermenters.[46] Gram-positive cocci were about 21.4% of the bacterial isolates namely staphylococcus aureus, coagulase-negative staphylococcus, enterococcus species and streptococcus species. Candida albicans was the major pathogenic fungus. Conversely, workers in the United States[20] as well as Israel[47] reported coagulase-negative staphylococci as the most common pathogenic isolate in nosocomial neonatal sepsis. This is in conformity with the evolutionary trend in the common causative pathogens over the past decades.
In summary, there appears to be a multi-centre variation in the predominance of either gram-positive cocci or gram-negative bacilli within NICUs in both developed and resource-limited countries.

Control strategies for nosocomial infections

Health care professionals act as vectors of disease despite their best intentions in patient care, and therefore play a role in propagating nosocomial infections.[48]
The hands, kits (gowns, gloves, masks, white coats etc.), and gadgets (stethoscopes, incubators, ventilators etc.) of the healthcare professional are confirmed vehicles of transmitting pathogenic microbes within the NICUs. Attention to simple preventive strategies which focus on these reservoirs of pathogens may thus reduce the transmission rates of nosocomial infections.
Infection control programs are generally cost-effective[49], but their implementation is frequently hindered by administrative bottle-necks, as well as non-compliance by health-care professionals.[48]

Since the major cause of nosocomial infections is the transmission of microbes from the hands of health-care personnel, hand washing or hand hygiene remains the most important measure for the control and prevention of such infections.[50]
Nonetheless in resource-limited countries, the major challenges of NICUs with respect to the burden of nosocomial infections are over-crowding by patients, understaffing with healthcare personnel, absence of a policy on rational antibiotic use, poor hygiene, as well as poor or non-existent infection control programs. Thus, the interplay of microbes, patients and the hospital environment (including antibiotic use and infection control practices) has led the emergence of antibiotic resistant pathogens.[21]

For instance, a survey of a labour unit contiguous to a newborn nursery in a West African hospital noted high cross infection rates due to poor hygiene and inappropriate use of antibiotics and disinfectants.[51]

Elsewhere in the Philippines, a study of two NICUs revealed that nosocomial transmission of drug-resistant pathogen (especially drug-resistant gram-negative bacilli) was intense;[52]the researchers were able to demonstrate that infection-control interventions were feasible and possibly effective in reducing neonatal nosocomial infection rates in resource-limited settings.

Therefore, any comprehensive control program in the NICUs in developing countries should aim to prevent or limit microbial entry into the nursery environment; prevent microbial multiplication; prevent spread of microbes between babies; as well as protect the newborn infants from developing infections.[53]

A summary of the components of these strategies is as follows:

- Strategies that can prevent the entry of microbes into the newborn nursery or NICU include entry restrictions, maintenance of a clean environment outside this hospital setting, as well as the promotion and practice of hand hygiene.
- Strategies that can prevent multiplication of microbes consist of regular cleaning, disinfection and sterilization of equipment and gadgets.
- Strategies that can prevent the spread of microbes between admitted newborn babies comprise prevention of overcrowding in incubators and open care systems, promotion of the use of disposable items rather than re-usable ones and increasing the nurse-to-patient ratio by adequate staffing.
- Strategies that will protect the newborn infant from developing infections include the promotion of breast feeding, maternal contact with their babies-even if preterm, early discharge or shortened hospital stay ,adequate cord/skin care and observing aseptic precautions during minor and major invasive procedures.

In resource-poor countries, these strategies are realistic and achievable provided there is commitment from administrators, as well as attitudinal change and compliance by care givers and healthcare personnel. One of the strategies that is not economically burdensome and yet proven to reduce nosocomial infection rates dramatically is hand hygiene. Hand hygiene is the term applied to either a thorough washing of hands with soap and water for at least 15 seconds or the application of 3 to 5mls of an alcohol-based antiseptic solution.

Infection control strategies: the economic rationale and their cost-effectiveness

The economic rationale for preventing nosocomial infections has been well established; [54, 55]these infections consume scarce health resources by prolonging patient's hospital stay. Cost-effective control strategies release these resources for alternative uses. If these resources have a value in an alternative use, then the strategy can be credited with generating cost savings. Although these control strategies are costly themselves, their *cost-effectiveness* is assessed by comparing the expense to the savings. When choices have to be made among several competing infection control strategies or interventions, the technique of incremental cost-effectiveness analysis has been applied;[56] where the cost of the strategies or interventions are represented in monetary terms and the benefits are measured in natural units common to all strategies or interventions under consideration. Several studies in developed countries have provided quantitative estimates of the cost savings from nosocomial infection strategies, especially hand-hygiene promotion programs.[57-61]

For instance, a study in a Russian NICU estimated that the added cost of one nosocomial blood stream infection ($1,100) would cover 3265 patient-days of hand antiseptic use ($0.34 per patient day).[57]In another study, it was estimated that cost savings achieved by reducing the incidence of Clostridium difficile-associated disease and MRSA infections far exceeded the additional cost of using an alcohol-based hand rub.[60] Pittet and colleagues[61] also estimated direct and indirect costs associated with a hand- hygiene program concluding that the strategy was cost saving if less than 1% of the reduction in nosocomial infections observed was attributed to improved hand- hygiene practices. Elsewhere in Canada, control measures including active surveillance cultures and contact precautions such as hand hygiene, use of gowns and gloves and thorough environmental cleaning were noted as cost-effective in reducing the rate of transmission of nosocomial infections.[62]

The adaptability of these proven cost-effective control strategies to developing countries (especially hand-hygiene programs) has been assessed in a pilot study sponsored by the World Health Organization in Africa. Allegranzi et al[63]reported the successful implementation and adaptation of the multimodal hand- hygiene improvement strategy in Bamako, Mali which consisted of introducing a locally-produced alcohol-based hand rub, monitoring hand- hygiene compliance, providing performance feedback and educating staff. The results clearly show that the cost-effective control strategies for nosocomial infections (with emphasis on hand hygiene) -demonstrated through several studies in developed countries- are equally feasible and effective in resource-limited settings such as sub-Saharan Africa.

Hand washing or hand hygiene- the cornerstone of infection control

The concept of hand washing as a method of infection control dates back to 1843 when Holmes suggested in a published essay that the degree of contagiousness of puerperal fever is related to patient-to-patient carriage by physicians and nurses.[64] Eighteen years later, Semmelweis discovered that hand hygiene was an effective means of reducing the mortality rate due to puerperal sepsis. By enforcing antiseptic practices among his students, he was able to reduce the mortality rate in the post-partum population from 12% to 1% within a two year period.[65]

The practice of hand washing or hand hygiene may appear simplistic but every health personnel should be aware that it involves six definite steps in order to achieve hand decontamination from pathogens.[53] (see figure 1).

Although liquid soap and water can effectively decontaminate hands, alcohol-based antiseptic hand rub or hand sanitizers provides the most effective decontamination for a wide variety of organisms.[66] In developing countries, alcohol-based antiseptics may become alternative means of hand hygiene because of their efficacy in reducing hand contamination and their ease of use, especially when sinks with elbow-operated tap and water supplies for hand washing are limited.[67]

Despite several observations showing that rates of nosocomial infection are substantially reduced when healthcare personnel acted in accordance with recommended guidelines for hand hygiene,[48, 68, 69] their compliance with hand washing remain consistently poor with physicians performing worse than other health workers.[70-73] Nevertheless, an institutionalized approach of routine monitoring, educational efforts and providing feedback to hospital staff can improve their hand- hygiene habits.[74,75]

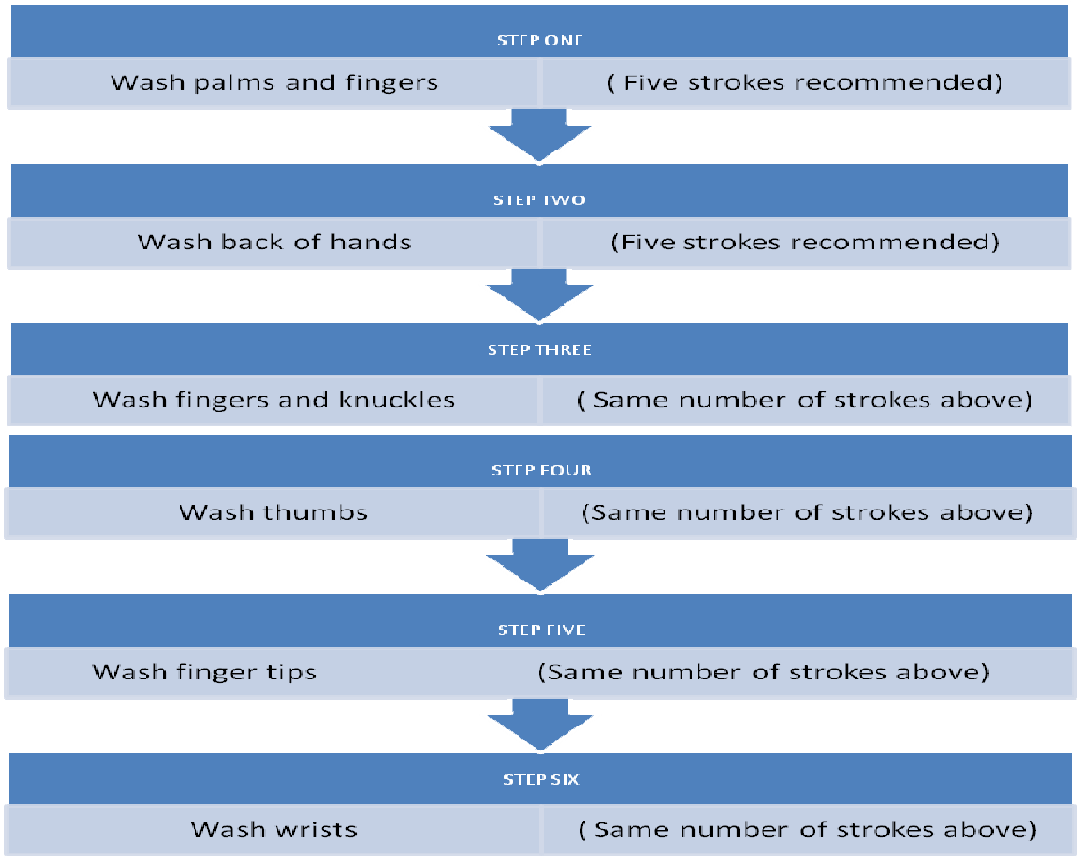
Other components of a successful system that can change the attitudes of healthcare workers to hand- hygiene practices include using reminders such as posters, establishment of policies and procedures for hand hygiene, reward and recognition of good performers, sanctions for non-compliance, as well as access to a safe continuous water supply at all outlets and readily available sinks, paper towels and the alternative use of alcohol-based sanitizers.[74]

When compared with other infection control measures such as the use of gloves, gowns and face masks, hand hygiene remains the cheaper, effective method of reducing nosocomial infections in NICUs within resource-limited settings. The major challenge in its implementation remains the scarcity of safe water in these settings. On the other hand, several studies show that gowning[76, 77] use of gloves,[78] and surgical face masks,[79] are not effective in limiting the transmission of nosocomial infections. Their routine use in infection control practices in developing countries is therefore not economically expedient.

Legend

The recommended six steps for effective hand washing[54]

Fig 1



- First wash for two minutes
- Before and after each patient contact for at least fifteen seconds

Conclusion

In resource-limited countries, hand washing or hand hygiene program is recommended as the most effective evidence-based strategy that will reduce the rates of nosocomial infection in NICUs. Because of poor compliance by healthcare workers, a multifaceted approach by healthcare institutions may help to improve their hand hygiene practices.

There should also be an administrative commitment to provide and sustain the basic components of a successful hand- hygiene program. Government should develop the will to meet the cost implications as the economic burden may not be comparable to the added financial expenditure of managing nosocomial infections.

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