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Healthcare-associated infections in neonatal units: lessons from contrasting worlds

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KEYWORDS
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Summary Neonatal intensive care units are vulnerable to outbreaks and sporadic incidents of healthcare-associated infections (HAIs). The incidence and outcome of these infections are determined by the degree of immaturity of the neonatal immune system, invasive procedures involved, the aetiological agent and its antimicrobial susceptibility pattern and, above all, infection control policies practised by the unit. It is important to raise awareness of infection control practices in resource-limited settings, since overdependence upon antimicrobial agents and co-existing lack of awareness of infection control is encouraging the emergence of multi-drug-resistant nosocomial pathogens. We reviewed 125 articles regarding HAIs from both advanced and resource-limited neonatal units in order to study risk factors, aetiological agents, antimicrobial susceptibility patterns and reported successes in infection control interventions. The articles include surveillance studies, outbreaks and sporadic incidents. Gram-positive cocci, viruses and fungi predominate in reports from the advanced units, while Gram-negative enteric rods, non-fermenters and fungi are commonly reported from resource-limited settings. Antimicrobial susceptibility patterns from surveillance studies determined the empirical therapy used in each neonatal unit. Most outbreaks, irrespective of the technical facilities available, were traced to specific lack of infection control practices. We discuss infection control interventions, with special emphasis on their applicability in resource-limited settings. Cost-effective measures for implementing these interventions, with particular reference to the recognition of the role of the microbiologist, the infection control team and antibiotic policies are presented.

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Introduction

The neonatal intensive care unit is an ideal situation to incorporate good infection control policy and practice, since it lends itself not only to the spread of severe infections but also to successful interventions. A collaborative effort between neonatologists and clinical microbiologists who take on the role of infection control can successfully mount a defence against healthcare-associated infections (HAIs). Clinical liaison between microbiologist and clinician is well established in developed countries, whereas in the developing countries such practices are yet to be widely recognized. One reason could be that microbiology results are often delayed in less technologically advanced laboratories, thus forcing the clinician to make empirical treatment decisions without consulting or depending on the microbiologist. However, technical advancement is not a prerequisite for appropriate selection of empirical antimicrobial agents, infection control practices or formulating antibiotic policies. In an environment where resources are scarce, it only requires determination and professional cooperation for suitable interventions to work.

This review on healthcare-associated neonatal infections studies the definitions, associated risk factors and the aetiological agents involved with their antimicrobial susceptibility patterns in two contrasting worlds. We discuss the microbiological and infection control intervention strategies that might help, even in resource-limited settings, to prevent the morbidity and mortality associated with HAI.

Levels of neonatal care: the contrast between developed and developing countries

Levels of neonatal care may be classified as shown in Box 1.

A large proportion of neonates in developing countries (63%) and in rural India (83%) are born at home, with poor facilities for safe and clean delivery by unskilled ‘dais’ or village health workers. Even larger hospitals with a high delivery rate do not have access to Level II neonatal care. No sick newborn care unit (SCNU), government or private, is available at district level in many provinces. The equipment and infrastructure are often limited and doctors are forced to select which babies will be admitted and offered facilities such as ventilators. Few state-owned centres are equipped with neonatal intensive care units (NICUs) and these are scattered across the country. Thus, in developing countries we are dealing with neonates with completely different demographic characteristics. Whereas the minimum gestational age of live-born babies managed in a NICU in developed countries is \( \leq 25 \) weeks with birthweights as low as 300 g, the average gestational age of live-born babies in developing countries is \( \geq 30 \) weeks with birthweights \( \geq 1000 \) g. In a study on anthropometry and body composition of south Indian babies at birth, the mean ± standard deviation (SD) birthweight of all newborns was 2.80 ± 0.44 kg. Financial constraints in developing countries limit the use of technical interventions, due to which very few neonates undergo invasive medical or surgical procedures, unlike reports from developed countries.

The available microbiological diagnostic facilities also vary from centre to centre. Semi-automated and automated culture systems are available only in a handful of tertiary care centres. The cost of providing these services to patients is borne by the family and is often prohibitive; most clinicians treat patients empirically. Microbiological results are particularly important in neonates as signs of sepsis are often non-specific. Hence, while financial constraints are difficult to resolve, we still have the option to utilize cost-effective, alternative interventions such as infection control, which by reducing the incidence of infection will decrease the overall morbidity and mortality in sick neonates. Successful field trials for home-based neonatal care have already been reported. We need to extend these achievements to healthcare settings.

Methods

We searched for articles on the PubMed database, using the index terms ‘hospital acquired infection’, ‘neonate’, ‘nosocomial infection neonate’, ‘neonatal care level’, ‘neonatal care India’. Reference lists of all articles retrieved were searched to obtain literature for the review. The articles were scrutinized to obtain a comparable and standard definition of nosocomial infection in neonates, inclusion and exclusion criteria used, aetiological agents involved, antimicrobial susceptibility patterns and infection control interventions. Within these search results, we reviewed articles mentioning infection control and antibiotic policies, with special reference to neonatal units in developing countries. Full text articles were scrutinized for a majority of English language papers; for a small number of articles we relied only on the published abstract. For foreign language studies we were able to quote only from the abstract published in English.
Normal microbiological flora of neonates

The foetus is exposed to a sterile environment in utero, provided no invasive procedures have been carried out on the mother, the membranes are intact until the onset of labour and there is no prolonged rupture of membranes. During the process of delivery, the neonate is exposed to several sources of microbes. These include the maternal genital tract followed by ambient air or water depending on the type of delivery, handling by healthcare personnel and the instruments used at resuscitation.

Rotimi and Duerden studied the development of bacterial flora of neonates during the first week of life. The predominant organisms in the gut, by the end of the first week, were anaerobes. Bifidobacteria were isolated from all the neonates. Bacteroides and clostridia were isolated from 78.3%. Enterococci were isolated from all neonates, enterobacteria from 82.6%, anaerobic cocci from 52.2%. Staphylococcus aureus was the predominant species isolated from the umbilicus; it was isolated from 21.7% of neonates on the first day rising to 87% by the sixth day and represented 49% of isolates from this site. Viridans streptococci (31.4% of isolates) were the commonest species recovered from the mouth. They were present from 8 h after birth. The authors also studied the development of microbial flora of preterm neonates. The numbers of infants studied were too small to

Box 1 Levels of hospital-based newborn services

Basic neonatal care (level I)

– Well-newborn nursery + evaluation and postnatal care of healthy newborns
– Neonatal resuscitation
– Stabilization of ill newborns until transfer to a facility at which specialty neonatal care is provided

Specialty neonatal care (level II)

– Special care nursery
– Care of preterm infants with birthweight ≥1500 g
– Resuscitation and stabilization of preterm and/or ill infants before transfer to a facility at which newborn intensive care is provided

Subspecialty neonatal intensive care (level III)

Level IIIA
– Restriction on type and/or duration of mechanical ventilation
Level IIIB
– No restrictions on type or duration of mechanical ventilation
– No major surgery
Level IIIC
– Major surgery performed on site
– No surgical repair of serious congenital heart anomalies that require cardiopulmonary bypass and/or ECMO for medical conditions
Level IIID
– Major surgery + surgical repair of serious congenital heart anomalies that require cardiopulmonary bypass and/or ECMO for medical conditions

ECMO, extra-corporeal membrane oxidation.

a Omphalocele repair, tracheo-oesophageal fistula or esophageal atresia repair, bowel resection, myelomeningocele repair, ventriculoperitoneal shunt.
draw any firm conclusions; their flora predominantly reflected the maternal genital tract.

In contrast, preterm and full-term babies born by Caesarean section were slow to acquire colonizing flora as compared to those born vaginally. The skin of infants born by Caesarean section is sterile soon after birth compared to neonates born by vaginal delivery. Bowel colonization of infants born by Caesarean delivery is also delayed. Colonization with bifidobacterium-like bacteria and lactobacillus-like bacteria reached levels similar to vaginally delivered infants at 1 month and 10 days, respectively.

Many HAIs result directly or indirectly from patient colonization; studies have shown that hospitalized patients are colonized rapidly with hospital flora. Colonizing flora such as Candida albicans in the gastrointestinal tract, vagina or perineal area, can precede infection when normal body defences are impaired through underlying disease, immunomodulating therapy, the use of invasive devices, or when the delicate balance of the normal flora is altered through antimicrobial therapy. However, antimicrobial therapy to eradicate colonizing microorganisms such as Pseudomonas aeruginosa is not beneficial and can propagate drug-resistant pathogens.

**Immune status of the neonate**

A newborn infant, particularly the preterm infant and to some extent the low birthweight infant, does not have a mature immune system and is often unable to mount an effective immune response. Natural barriers, such as the acidity of the stomach or the production of pepsin and trypsin that maintain sterility of the small intestine, are not fully developed until 3–4 weeks after birth. Membrane protective IgA is missing from the respiratory and urinary tracts, and unless the newborn is breast-fed, is absent from the gastrointestinal tract as well. On a cellular level, there is decreased ability of leukocytes to concentrate where necessary. These leukocytes are less bactericidal and phagocytic. At the humoral level, the newborn has low or non-existent levels of the immunoglobulin antibodies IgM, IgE and IgA. The neonate is born with IgG antibodies acquired from the mother. However, it is important to note that passive transfer of maternal antibodies does not take place till 29 weeks of gestation. This has implications for preterm infants born 25–29 weeks of gestation; they are susceptible to infection despite the mother’s antibody status. There is a slow rise of immunoglobulin levels after 3 months of age to levels of older children.

**Definition of healthcare-associated infection**

Before embarking on a review of nosocomial infections, we reviewed the definitions of nosocomial infections used in various studies.

At the outset, the National Nosocomial Infections Surveillance System (NNIS) of the Centers for Disease Control and Prevention (CDC), USA defines nosocomial infection as a localized or systemic condition (1) that results from adverse reaction to the presence of an infectious agent(s) or its toxin(s) and (2) that was not present or incubating at the time of admission to the hospital.

**Limitations encountered during the review process**

In the neonate, the definition of an HAI is complicated by the fact that neonates can acquire infection from the maternal genital tract during birth. For this reason, neonatal infections are often classified as early onset (usually 0–7 days after birth) and late onset (>7 days after birth). Some authors also classify them as ≤72 h after birth and >72 h after birth. It is interesting to note that the CDC includes infections acquired from the maternal genital tract in their surveillance of nosocomial neonatal infection. Several investigators have found these criteria unsatisfactory.

For the purposes of this review, we have considered only those studies that have excluded infections acquired directly from the maternal genital tract; we found that the definition of nosocomial infections varied between studies and were often related to time of acquisition. The Dutch group have modified the CDC criteria to include infections occurring in the neonatal unit 24–48 h after admission. In some studies, infections which manifested after the patient was in the hospital for ≥48 h and those infections which developed within a period of 7 days after discharge from the hospital were considered nosocomial.

In other studies, all neonates residing for ≥3 days in a hospital unit were included. Nosocomial transmission of candida in neonates was considered if the neonate showed negative surveillance cultures at birth and positive cultures from one week later, until death or discharge. Shankar et al. also recommend using surveillance cultures to differentiate endogenous colonization from nosocomial acquisition.

We believe that a consistent and universally accepted case definition of HAI in the neonate is important because it offers uniformity of data...
across centres and facilitates a standardized measurement of outcomes. Many studies that we reviewed did not have clear-cut case definitions with clearly stated inclusion and exclusion criteria; when they did, they varied from centre to centre.

Other common limitations were inadequate sample size, or variability of denominator data wherein some authors reported number of infections per 100 patients (attack rate) or the number of infections per 1000 patient-days (incidence density). Annual incidence per 100 000 live births and per 100 NICU discharges have also been used. Absence of robust statistical analysis and the inclusion of anecdotal case reports were also limitations. Some authors acknowledge the lack of technical equipment to report viral, fungal and parasitic causes of HAIs.

Results

Risk factors for HAIs in neonates

Neonates present with their own unique risk factors that predispose them to acquisition of HAI. The vulnerability of the neonate, particularly the preterm neonate, is directly linked to an immature immune system. This is the single most important host-related factor that predisposes them to infection.

Neonatal age itself is a risk factor for HAI [odds ratio (OR) 5.89; 95% confidence interval (CI): 2.96–11.58; P < 0.05]. In another study, admission to the neonatal unit, rather than age at admission, was associated with increased risk of HAI (P < 0.001). The overall nosocomial infection rate was positively correlated with average length of stay in high-risk nurseries (r = 0.6, P < 0.05).

Preterm gestational age (<32 weeks) was a risk factor in 26–60% neonates with bacterial, viral and fungal HAI. The percentage of neonates with low birthweight (1.5–2.5 kg) and with very low birthweight (1.0–1.5 kg) who acquired HAI was 55.5 and 28.2 to 29.6% respectively. Infection, including HAI, was the most common cause of death in extremely low birthweight (<1.0 kg) neonates and septicaemia (bacterial and fungal) was the most common presentation (68.4%). Male sex was a predisposing factor for nosocomial infections (P < 0.05). The male predominance in neonatal sepsis has suggested the possibility of an X-linked factor in host susceptibility.

Underlying medical conditions such as chronic lung disease, gastro-oesophageal reflux, history of neonatal respiratory distress, maternal infection and congenital heart disease predisposed to HAIs in 4.3–26.1% of neonates. A high complexity score, which categorizes procedures by severity of illness and technical complexity, was associated with increased incidence of HAI in neonates after cardiac surgery (OR: 4.03; 95% CI: 1.87–8.43; P < 0.05). PRISM (Pediatric Risk of Mortality) score of >25 was also related to neonatal HAI (crude OR: 8.90; 95% CI: 3.49–22.76; P < 0.001). The Clinical Risk Index for Babies (CRIB) score shows that nosocomial bacteraemia is independently associated with low birthweight and preterm neonates. Lack of maternal antibodies was a risk factor for infection with unusual rotavirus strains.

Factors relating to healthcare personnel, practices and the environment are often overlooked, and yet remain the most obvious and inexpensive area of intervention. Indeed, the most common route of spread of nosocomial pathogens is person-to-person transmission within the unit and during transfer of patients between units. Such incidents have been linked with outbreaks of bacterial and viral infection in the NICU.

The most common iatrogenic factor contributing to neonatal HAIs is hands of healthcare workers. Intervention in the form of simple handwashing procedures and infection control practices has prevented outbreaks, as reported in many studies.

During the process of delivery, the neonate is exposed to several sources of microbes. Medical devices such as umbilical catheters, central venous catheters, urinary catheters and endotracheal tubes are commonly used in the NICU. Central venous catheters contributed to 48.9% of HAIs in one study and was a significant risk factor (P < 0.05) in others. The nosocomial infection rate was higher in neonates subjected to device use (r = 0.26, P < 0.02). About 10.8% of catheterized patients developed hospital-acquired urinary tract infection (UTI). The duration of ventilation was also related to the acquisition of HAI.

Reuse of single-use items, a common though unsound practice in many units, has led to outbreaks of HAI. Endotracheal tubes and mucous extraction suction catheters soaked in Hibitane were associated with HAI in the labour room and the special care baby unit. Baby placement services, resuscitation equipment and cleansing solutions have also been implicated in HAI.

An environmental risk factor often overlooked is related to the seasonal variation in the incidence of neonatal HAI. Factors such as warm climate have been associated with a rise in colonization rates with Enterobacter spp.
use of nursery air conditioners propagates airborne dissemination of Acinetobacter spp. and has been associated with acinetobacter-related bloodstream infections. Bacteria in ambient air have been reported to colonize the conjunctiva in neonates.

Agent factors contributing to HAI relate to the aetiological agents implicated in infection. Infection with drug-resistant organisms plays a significant role in the outcome of HAI in all patients, irrespective of their gestational age and underlying condition. Hospitalization leads to colonization of the skin and gastrointestinal tract with resistant flora found in hospitals and subsequent bloodstream infection, when the skin or mucosa is abraded. Studies have reported that administration of prophylactic antibiotics to neonates can increase the incidence of HAI with drug-resistant pathogenic micro-organisms. About 64.8%–100% of neonates presenting with HAI had received prior broad-spectrum antibiotics.

Clinical presentation of HAI in neonates

A summary of the most commonly reported neonatal HAI is described in Table I. A review of the findings of these studies is hampered by the variation and sometimes lack of denominator data. The reader is advised to study these reports with caution, taking into consideration the limitations mentioned earlier.

Common aetiological agents of neonatal HAIs

Healthcare-associated infections in the neonatal unit cover the entire spectrum of organisms: bacterial, fungal, viral and rarely parasitic. A review of healthcare-associated bacterial (Table II), fungal (Table III), and viral (Table IV) infections is summarized in the relevant tables.

Fortunately parasitic nosocomial infections are rare. There have been isolated reports of babesiosis transmitted by blood transfusion in neonates. Among four neonates transfused with blood from asymptomatic babesia-infected donors, two (50%) became parasitaemic, of whom only one developed symptoms of babesiosis.

It is interesting to note that Gram-negative fermenters (E. coli, Klebsiella spp.) and non-fermenting Gram-negative rods such as Acinetobacter spp. and Pseudomonas spp. have established themselves as predominant causes of serious neonatal infections in the Indian subcontinent (Table II). In contrast, the predominant organisms isolated from invasive neonatal infections in technologically advanced countries are Gram-positive cocci.

| Clinical presentation | % of all infections reported |
|-----------------------|-----------------------------|
| Septicaemia | 25%–50% |
| According to the National Neonatal Perinatal Database (2000) in India the incidence of neonatal septicaemia is 24/1000 live births |
| Lower respiratory tract infections | 50%–75% |
| Necrotizing enterocolitis/perforation | >75% |
| Meningitis | 3%–10% |
| Skin (central venous catheter site, operation wound, umbilicus) infections | 15%–30% |
| Arthritis | 100% |
| Device (ventriculo-peritoneal shunt) | 2%–15% |
| Urinary tract infections | 35%–75% |
| Eye infections | 1.5%–6% |
| Oropharyngeal infections | 1%–30% |
| Gastroenteritis | 2%–6% |
| Upper respiratory tract infections | <1% |
| Ear infections | 3%–20% |

Healthcare-associated neonatal infections

Table I Clinical presentation of neonatal healthcare-associated infections

| Clinical presentation | % of all infections reported |
|-----------------------|-----------------------------|
| Septicaemia remains the most common cause of neonatal mortality in the NICU. According to the National Neonatal Perinatal Database (2000) in India the incidence of neonatal septicaemia is 24/1000 live births |
| Lower respiratory tract infections | 25%–50% |
| Necrotizing enterocolitis/perforation | 50%–75% |
| Meningitis | >75% |
| Skin (central venous catheter site, operation wound, umbilicus) infections | 3%–10% |
| Arthritis | 15%–30% |
| Device (ventriculo-peritoneal shunt) | 100% |
| Urinary tract infections | 2%–15% |
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| Oropharyngeal infections | 1.5%–6% |
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| Upper respiratory tract infections | 1%–30% |
| Ear infections | <1% |

Healthcare-associated infections in the neonatal unit cover the entire spectrum of organisms: bacterial, fungal, viral and rarely parasitic. A review of healthcare-associated bacterial (Table II), fungal (Table III), and viral (Table IV) infections is summarized in the relevant tables.
The reason for this difference is probably multifactorial and could be due to gestational age of the babies involved, the use of invasive devices (central vascular catheters and shunts), ambient moisture, humidity and the prevalent flora in the unit. Evidence supporting these risk factors has been discussed elsewhere in the review and probably merits further evaluation.

Of all the fungal infections reported in neonatal patients, *Candida* spp. cause significant mortality and morbidity in the neonatal unit (Table III) and will be discussed in some detail here. Although the source of *C. albicans* infection in the NICU is often considered to be endogenous, molecular typing studies have shown that nosocomial transmission of *C. albicans* is the predominant mode of acquisition. The nosocomial acquisition of *C. albicans* is related to cross-contamination via the hands of healthcare workers or parents and the use of contaminated equipment. In one study, retrograde medication syringe fluids were significantly more likely to be contaminated with candida than other fluids being administered to the infants ($P < 0.001$). Candidaemia was significantly associated with total parenteral nutrition ($P = 0.04$) and retrograde medication administration ($P = 0.02$). Central vascular catheters, steroid administration, endotracheal intubation and H2-blockers have also been reported as risk factors for systemic infections.

### Table II  Hospital-acquired bacterial infections

| Organism                      | Lessons learnt                                                                 | % cause of infection |
|-------------------------------|-------------------------------------------------------------------------------|---------------------|
| *Klebsiella* spp.             | Nosocomial surgical site infections in neonates following contamination with endogenous flora. | $2.5–10\%^{18,40}$ |
|                               | Also implicated in sepsis, meningitis, conjunctivitis, parotitis.              | $20–60\%^{18,30,61}$|
| *Enterobacter* spp.           | Bloodstream infection due to contamination of surgical site with endogenous flora. | $3–20\%^{18,40}$   |
|                               | Mortality in surgical infections 100%.                                         | $50\%^{61}$         |
| *Pseudomonas* spp.            | Cause of sepsis, pneumonia, urinary tract infection.                          | $10–16\%^{18,25,61}$|
| *Escherichia coli*            | Rate of antimicrobial resistance was higher in the nosocomial strains of *E. coli* compared to community-acquired strains ($P < 0.05$). | $4.3–6\%^{18,40}$  |
|                               | Mortality in surgical infections 100%.                                         | $>40\%^{61}$        |
| *Acinetobacter* spp.          | Implicated in colonization as well as infection; 56% mortality reported with the latter; mortality in surgical infections 100%. | $6–12\%^{18,33}$   |
|                               | Mortality in surgical infections 100%.                                         | $>25\%^{23}$        |
| *Serratia* spp.               | Cause of sepsis in neonates with surgical wounds. 3–35%                        | $18,61$             |
|                               | Also a cause of meningitis, pneumonia, umbilical wound infection, conjunctivitis. |                     |
| *Stenotrophomonas maltophilia*| Cause of sepsis in neonates with surgical wounds. 4%                          | $18$                |
| Coagulase-negative            | Most common pathogen causing HAI in the surgical neonatal unit. Meticillin resistance in CoNS was 92.3% and mortality 16%. | $3–11\%^{18,25}$   |
| *staphylococcus* (CoNS)       | Meticillin resistance 72.7%.                                                  | $45–60\%^{15,21,40}$|
| *S. aureus*                   | Mortality due to sepsis 24%. *MRSA* caused 38.8% of HAI in neonates with mortality of 28.6%. | $4–10\%^{15,18,21,40}$|
|                               | Central venous catheter was the source of infection with *S. aureus* in 7/8 infected neonates. | $>35\%^{17,25}$    |
| *Enterococcus* spp.           | No colonization with vancomycin-resistant enterococci (VRE) was noted in neonates despite prior vancomycin therapy. | $5–6\%^{18,25,40}$|
|                               | Mortality in surgical neonatal unit.                                           | $>23\%^{21}$        |
| *Bacteroides* mitis           | Common cause of bloodstream infection in the surgical neonatal unit.           | $2.5–10\%^{21,40}$ |
| Group B beta haemolytic       | Cause of surgical site infections in neonates. 7.6%                          | $21$                |
| *streptococcus* (GBS)         | Relatively uncommon cause of HAI in neonates in India.                        | $7.9\%^{40}$        |
|                               | No cases of late-onset disease due to GBS reported from India.                 |                     |

HAI, hospital-acquired infection; *MRSA*, meticillin-resistant *Staphylococcus aureus*. 

(coagulase-negative staphylococci, Group B streptococcus). The reason for this difference is probably multifactorial and could be due to gestational age of the babies involved, the use of invasive devices (central vascular catheters and shunts), ambient moisture, humidity and the prevalent flora in the unit. Evidence supporting these risk factors has been discussed elsewhere in the review and probably merits further evaluation.

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### Table III  Hospital-acquired bacterial infections

| Organism                      | Lessons learnt                                                                 | % cause of infection |
|-------------------------------|-------------------------------------------------------------------------------|---------------------|
| *Klebsiella* spp.             | Nosocomial surgical site infections in neonates following contamination with endogenous flora. | $2.5–10\%^{18,40}$ |
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HAI, hospital-acquired infection; *MRSA*, meticillin-resistant *Staphylococcus aureus*.
fungal infections in neonates. Other risk factors include prematurity, low birthweight and use of broad-spectrum antibiotics. Complications of candidaemia such as endocarditis and uveitis have been reported in neonates. The onset of endocarditis was related to persistant candidaemia. Fungal endocarditis was present in 13.7% neonates with persistent disease (>5 days of candidaemia) and 3.7% patients with non-persistent disease (OR: 4.19), while uveitis developed in 3.4% patients. Mortality in neonates with persistent disease was comparable to the mortality in neonates with non-persistent disease.

Viruses account for about 1% of infections in hospitalized neonates. The most common viral infections are due to enterovirus/parechovirus (Table IV). Enteroviruses were responsible for the highest mortality and development of serious sequelae. Respiratory syncytial virus (RSV) is the second most common virus causing infections in hospitalized neonates (14–37%). Respiratory viruses were diagnosed in 29.5% of neonates on mechanical ventilators; the most frequent was RSV (14.1%), followed by influenza A virus (10.2%). In another study, nosocomially acquired RSV infection was present in 37% of neonates, 54.3% had an underlying condition predisposing to severe disease and 13% died. Human parainfluenza type 3 is the most common cause of bronchiolitis and pneumonia after respiratory syncytial virus. Parainfluenza type 3 virus was isolated in six of 17 neonates cultured (five symptomatic patients and one asymptomatic patient). Eighteen of 52 nursing personnel had been ill during the previous week, concomitantly with cough and nasal congestion. Nosocomial transmission of rotavirus in neonates has been reported. The onset of acute diarrhoea due to rotavirus in two neonates was followed by five neonates developing gastroenteritis with the same strain of rotavirus. In another study, in 51% of inpatients with nosocomial gastroenteritis, the causative agent was rotavirus and 26% of those were premature neonates.

**HAIs and resistance to antimicrobial agents**

Compared to community-acquired infections, HAIs are often caused by multi-drug-resistant pathogens. In this section we concentrate on reports from the subcontinent and other resource-poor settings. In a retrospective study of bacterial isolates from cases of neonatal sepsicaemia over a period of 5 years, there was a significant rise in the incidence of drug-resistant *Acinetobacter* spp. and *P. aeruginosa*. The incidence rate of acinetobacter septicaemia in another study was 11.1/1000 live births. Other studies have also documented *Acinetobacter* spp. as emerging neonatal pathogens.

**Table III**  
Hospital-acquired fungal infections

| Fungi | Lessons learnt |
|-------|----------------|
| *C. albicans*<sup>26,32,80,81</sup> | Important causes of non-persistent candidaemia, persistent candidaemia, endocarditis, uveitis. Molecular epidemiology suggests nosocomial rather than maternal transmission of *C. albicans* in neonates.  
Source of infection was central venous catheter. |
| Non-albicans *Candida* spp.<sup>a,21,25,32,46,80,82</sup> | Cause of candidaemia, endophthalmitis, endocarditis, meningitis, peritonitis. Source of infection was central venous catheter. |
| *Rhodotorula mucilaginosa*<sup>83</sup> | Outbreak (*N* = 4) of indwelling catheter-related sepsicaemia in NICU. Related to birthweight, gestational age, duration of parenteral nutrition, antibiotic therapy and prophylactic fluconazole. |
| *Rhizopus microsporus*<sup>84</sup> | Outbreak of cutaneous infection in preterm neonates (*N* = 4). Source traced to wooden tongue depressors used in the nursery as splints for intravenous and arterial cannulation site. The combination of warm, humid conditions in neonatal incubators, particularly in association with occlusive dressings, also favours cutaneous fungal infections. |

NICU, neonatal intensive care unit.

<sup>a</sup> Non-albicans *Candida* spp. included *C. parapsilosis, C. tropicalis, C. lusitaniae, C. glabrata, C. krusei, C. guillermondii.*
less susceptible to the commonly used antibiotics, such as ampicillin (20.7%), amoxicillin (25.4%), gentamicin (56.8%), ceftazidime (28.4%) and cefotaxime (44.8%). These organisms were more susceptible to imipenem (76.4%), amikacin (77.7%), ofloxacin and ciprofloxacin (88.1%). Other workers found third-generation cephalosporins and aminoglycosides such as netilmicin to be effective in the treatment of neonatal sepsis. At the same time, studies have also shown that administration of antimicrobial prophylaxis, presumed to prevent HAIs, can be a putative risk factor in itself for HAI.

Single-centre studies have shown that probiotics containing anaerobic bacteria may reduce the rate and severity of necrotizing enterocolitis. Antifungal agents
Flucanazole has been recommended as prophylaxis against systemic fungal infections in preterm low birthweight infants. However, other workers have found no resurgence of fungal infection after cessation of prophylactic fluconazole use. There is also concern about emergence of resistance to fluconazole. In an investigation into the resurgence of bloodstream infections due to C. parapsilosis in one unit, after the institution of fluconazole prophylaxis, primary resistance to fluconazole was not detected. Others propose a twice weekly dosing of prophylactic fluconazole to decrease candida colonization, invasive infection, cost and patient exposure in high-risk preterm infants weighing <1000 g at birth; the lower and less frequent dosing may even delay or prevent the emergence of antifungal resistance.

There are reports of C. albicans resistance to fluconazole (12.5%) and amphotericin-B (25%) in studies from India. Newer antifungal agents, including voriconazole and caspofungin, show promise in the treatment of potentially fatal fungal infections in neonates and additional controlled studies are indicated to evaluate their role.

Principles of infection control in the neonatal unit
The existing evidence base for infection control practices specifically for the neonatal unit is described in Table V. Important lessons in infection control can be learnt from published accounts of specific outbreaks. In addition to the outbreaks documented in Tables III and IV, we have selected other outbreak reports that we believe reinforce the infection control message (Table VI).

Environmental surveillance is not routinely recommended since pathogens present in the inanimate NICU environment, e.g. floors, walls, sink-drains or furniture are not associated with...
Only three NICU sites, namely baby placements, resuscitation equipment and various cleansing solutions, were found to be significantly associated with HAIs ($P < 0.001$) in one study. The relative risk of infection was greatest if baby placement sites were colonized (odds ratio = 7.48; $P < 0.01$). This reinforces the need for scrupulous cleaning regimens rather than adopting a policy of routine environmental surveillance.

However, environmental cultures may play a role in specific outbreak situations. Outbreak strains of *Salmonella worthington* were isolated from the baby warmer mattress, baby cot, suction machine bottle and wall of the refrigerator. The role of surveillance cultures to predict the onset of nosocomial infections in neonates undergoing invasive procedures, such as exchange transfusion, has been studied. The authors found that except for staphylococci, the flora from umbilical stump and umbilical vein blood in asymptomatic neonates was similar to the flora from infected neonates.

Table V  Recommended infection control practices

| Policy                                      | Practice                                                                                                                                 |
|---------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Infection control policy and practice       | Handwashing, gown, gloving, mask, cohorting uninfected neonates, isolation of infected neonates, short natural fingernails in healthcare staff, thorough cleaning, better patient care facilities, strict winter visiting policies. |
| Disinfection and maintenance of equipment   | Surface disinfection; disinfection of ventilators.                                                                                      |
| Single-use items                            | Use of disposable endotracheal tubes; mucous extraction suction catheters and hand towels. An expensive option in the resource-poor setting. |
| Infrastructure and staffing                 | Regular water supply; improve staff:patient ratio; adequate infrastructure; sick leave policy for staff.                                   |
| Surveillance and monitoring                 | Aggressive case finding, notification of contacts; screening cultures for antibiotic resistance; screening for MRSA; surveillance cultures of the environment in outbreak settings; surveillance and monitoring for resistant flora. |
| Antibiotic policy                           | Adoption of an evidence-based antibiotic policy in the neonatal unit; refers to a 10-point plan on antibiotic use.                         |

MRSA, meticillin-resistant *Staphylococcus aureus*.

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‘Intensive care’ need not be synonymous with ‘invasive care’. In the presence of constraints such as lack of trained staff, intermittent power supply or lack of disinfection between their use, incubators and other medical devices can be a risk factor for HAI. In these situations kangaroo care provided by the mother has emerged as a cost-effective and widely accepted style of caring for an infant in hospital. In a study from India, there was significant improvement among the kangaroo care group compared with the conventional group, in terms of hypothermia (10/44 vs 21/45, $P < 0.01$), higher oxygen saturations (95.7 vs 94.8, $P < 0.01$) and decrease in respiratory rates (36.2 vs 40.7, $P < 0.01$). However, there was no statistically significant difference in the incidence of hyperthermia, sepsis, apnoea, onset of breastfeeding and hospital stay in the two groups. Further studies are needed to evaluate the role of kangaroo care and the incidence of HAI in neonates.

**Discussion**

The role of microbiology in the detection, epidemiological analyses and prevention of HAIs cannot be overemphasized, whether the unit is one that benefits from being resource rich or resource poor. In a setting where most physicians are reluctant to use first-line agents, due to misleading or lack of sufficient susceptibility data, a qualified microbiologist is indispensable. Communication between microbiologist and neonatologist helps in deciding the most probable pathogen and in initiating the most appropriate antimicrobial therapy. The formulation of a mutually agreed antibiotic policy at community, institutional and national levels is imperative.
An infection control team (ICT) comprising an infection control nurse or an infection control trained link nurse in the NICU, a neonatologist/physician and a microbiologist must actively participate in outbreak management and infection control policy issues. In turn, it is mandatory that microbiologists balance their focus equally on diagnostic as well as clinical microbiology. Microbiological influence and involvement can be enhanced if the microbiologist joins regular clinical ward rounds and helps to raise awareness among healthcare professionals regarding all aspects of infectious disease management. Education and training is an important remit of the ICT. Besides training of healthcare staff we believe it is important to provide training to empower the mother. As the main carer in the family her education is vital; if she can be made aware of the rationale behind the microbiologist or neonatologist’s advice, she will be in a stronger position to participate in the wellbeing of herself and the baby.

Even as huge efforts are underway to halt the misuse of antimicrobial agents, issues regarding antimicrobial resistance in pathogens are less important to the lay public. As long as these essential drugs are available over-the-counter in many countries, all efforts in any other part of the world toward preventing their misuse will be undermined. In addition, a number of privately funded laboratories have sprung up in several cities and towns in developing countries. They lack quality assurance and the personnel who work in identifying pathogens and reporting susceptibility are not trained adequately in quality control methods.

In resource-limited settings, as in technologically advanced units, advising that we wash our hands and use the most appropriate antimicrobial agent may be more valuable than suggesting expensive tools for molecular testing. We provide a simple, resource-efficient template for the investigation and maintenance of infection control in the clinical setting (Box 2). In the present era of global information sharing, professionals working in the area of infection control need not feel isolated. There are several useful web tools that provide practical information and guidance; our own

### Table VI Outbreak investigations that provide valuable lessons in infection control

| Organism               | Outbreak investigation                                                                                       |
|------------------------|-------------------------------------------------------------------------------------------------------------|
| **Klebsiella spp.**    | Outbreak of septic arthritis (N = 17) linked to contaminated cover sheets.                               |
| **P. aeruginosa**      | Epidemiological evidence of an association between acquiring P. aeruginosa bloodstream infection in neonates and exposure to nurses with long and artificial fingernails. Short natural fingernails is a policy that is essential to reduce the incidence of HAI in neonates. |
| **Serratia marcescens**| An outbreak of invasive S. marcescens in the NICU (N = 14). Molecular tests showed that a vast majority of clinical and environmental isolates (from hands of nurse, handwashes and disinfectants) belonged to the same clonal type. Cohorting of non-infected neonates, isolation of colonized and infected neonates, glove use and handwashing controlled the outbreak. Outbreak (N = 9) of S. marcescens in the NICU. Epidemic strain isolated from handwashes and doors of incubators. Strict handwashing, disinfection of incubators, cohorting and isolating patients controlled further transmission. |
| **Acinetobacter spp.** | During an outbreak, isolates with similar antibiogram were recovered from intravenous catheter and washbasin. |
| **Listeria monocytogenes** | Neonatal cross-infection due to contaminated equipment resulted in sepsis and central nervous system disease. |
| **Salmonella worthington** | Outbreak of seven cases, six fatalities. Equipment and environment were the source of outbreak. Outbreak was controlled through cleaning and fumigation. |
| **Shigella sonnei**    | Transmission among nursery staff.                                                                         |
| **Enterotoxigenic E. coli (ETEC)** | Outbreak involved preterm neonates (N = 16); surveillance cultures of swabs from the utensils used to prepare milk feed, culture of the formula feed and all items handled by one particular cook were undertaken. The cook’s hand swabs and faecal sample yielded growth of ETEC. The outbreak was controlled by appropriate therapy and institution of proper measures of hygiene. |
| **Enterobacter spp.**  | Outbreak (N = 30 and N = 10) of Enterobacter cloacae septicaemia traced to preceding bladder catheterization and/or parenteral nutrition solution, respectively. |

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Box 2 Ten cost-effective steps towards infection control in the neonatal unit

1. Ensure a strict protocol for hygienic handwashing and provision of clinical handwash basins or sinks
2. Involve the microbiologist in the planning stages or when refurbishing the unit; advice on physical setting of the unit and general layout of cots, bays, sinks will impact on infection control
3. Provision of side rooms and bays for the isolation of infected babies or protection of healthy neonates
4. Provide training and advice regarding environmental cleaning; ensuring that all surfaces are maintained clean and dry
5. Create an infection control policy document and a rational antibiotic policy that is constantly reviewed
6. Appoint an infection control team (ICT) comprising a microbiologist, neonatologist, infection control nurse/liaison nurse trained in infection control
7. Support the ICT in the management of infectious diseases and in promoting infection control practices
8. Provide education and training of unit staff in infection control
9. Take the lead in outbreak investigation and control
10. Install a laboratory surveillance system for alert organisms (i.e. important pathogens causing hospital-acquired infections and their susceptibility patterns)

policy is available free of charge at www.infection-controlservices.co.uk/.

References

1. Stark AR. Levels of neonatal care. Pediatrics 2004;114:1341–1347.
2. Bang AT, Bang RA, Baitule SB, Reddy MH, Deshmukh MD. Effect of home-based neonatal care and management of sepsis on neonatal mortality: field trial in rural India. Lancet 1999;354:1955–1961.
3. Fernandez A, Mondkar JA. Status of neonatal intensive care units in India. J Postgrad Med 1993;39:57–59.
4. Miljevski I, Norheim OF. My job is to keep him alive but what about his brother and sister? How Indian doctors experience ethical dilemmas in neonatal medicine. Developing World Bioeth 2006;6:23–32.
5. Muthayya S, Dwarkanath P, Thomas T, et al. Anthropometry and body composition of south Indian babies at birth. Indian Pediatr 2006;9:896–903.
6. Rotimi VO, Duerden BI. The development of the bacterial flora of normal neonates. J Med Microbiol 1981;14:51–62.
7. Rotimi VO, Olowe SA, Ahmed I. The development of bacterial flora of premature neonates. J Hyg (Lond) 1985;94:309–318.
8. Sarkany I, Gaylarde CC. Skin flora of the newborn. Lancet 1967;1:589–590.
9. Gronlund MM, Lehtonen OP, Eerola E, Kero P. Fecal microflora in healthy infants born by different methods of delivery: permanent changes in intestinal flora after cesarean delivery. J Pediatr Gastroenterol Nutr 1999;28:19–25.
10. Jarvis W. The epidemiology of colonization. Infect Control Hosp Epidemiol 1996;17:47–52.
11. Beloborodova NV, Vostrikova T. Characteristics of fauces microflora in children treated in intensive care units. Antibiot Khimioter 1998;43:16–22.
12. Klein O. Bacterial sepsis and meningitis. In: Remington SJ, Klein OJ, editors. Infectious diseases of the fetus and newborn infant. 5th ed. Philadelphia: W.B. Saunders Company; 2001. p. 943–984.
13. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control 1988;16:128–140.
14. Aurangzeb B, Hameed A. Neonatal sepsis in hospital-born babies: bacterial isolates and antibiotic susceptibility patterns. J Coll Physicians Surg Pak 2003;13:629–632.
15. van der Zwart WC, Kaiser AM, van Elburg RM, et al. Nosocomial infections in a Dutch neonatal intensive care unit: surveillance study with definitions for infection specifically adapted for neonates. J Hosp Infect 2005;61:300–311.
16. Malik A, Hasani SE, Khan HM, Ahmad AJ. Nosocomial infections in newborns. Indian Pediatr 2001;38:68–71.
17. Denniston S, Riordan FA. Staphylococcus aureus bacteremia in children and neonates: a 10 year retrospective review. J Infect 2006;53:387–393.
18. Levy I, Ovdia B, Erez E, et al. Nosocomial infections after cardiac surgery in infants and children: incidence and risk factors. J Hosp Infect 2003;53:111–116.
19. Fowlie PW, Gould CR, Parry GJ, Phillips G, Tarrow-Mordi WD. CRIB (clinical risk index for babies) in relation to nosocomial bacteraemia in very low birthweight or preterm infants. Arch Dis Child Fetal Neonatal 1996;75:F49–F52.
20. Mahieu LM, Buitenweg N, Beutels P, De Dooy JJ. Additional hospital stay and charges due to hospital-acquired infections in a neonatal intensive care unit. J Hosp Infect 2001;47:223–229.
21. Shankar KR, Brown D, Hughes J, et al. Classification and risk-factor analysis of infections in a surgical neonatal unit. J Pediatr Surg 2001;36:276–281.
22. Coovadia YM, Mayosi B, Adhikari M, Solwa Z, van den Ende J. Hospital-acquired neonatal bacterial meningitis: the impacts of cefotaxime usage on mortality and of
amikacin usage on incidence. Ann Trop Paediatr 1989;9:
233–239.
23. Srivastava S, Sen MR, Kumar A. A Study on Microbial Etiology and Diagnosis of Neonatal Septicemia, Thesis submitted for the course of MD in Microbiology. Varanasi, India: Central Library, Banaras Hindu University; 2005.
24. Rodríguez D AB, Park BJ, Cuenca-Estrella M, et al. Barcelona Candidemia Project Study Group. Candidemia in neonatal intensive care units: Barcelona, Spain. Pediatr Infect Dis J 2006;25:224–229.
25. Usukura Y, Igarashi T. Examination of severe, hospital acquired infections affecting extremely low birthweight (ELBW) infants. Pediatr Int 2003;45:230–232.
26. Reef SE, Lasker BA, Butcher DS, et al. Nonperinatal nosocomial transmission of Candida albicans in a neonatal intensive care unit: prospective study. J Clin Microbiol 1998;36:1255–1259.
27. Sabatino G, Verrotti A, de Martino M, Fusilli P, Pallotta R, Chiarelli F. Neonatal suppurative parotitis: a vanishing disease? Eur J Pediatr 1998;157:913–916.
28. Bonatti H, Guggenbacher JP, Hager J. Treatment of nosocomial infections in children undergoing antimicrobial chemotherapy. Infection 1990;18:302–306.
29. Pillay T, Pillay DG, Hoosen AA, Adhikari M, Nowbath V. Utility of surveillance bacterial cultures in neonatal exchange blood transfusions. J Hosp Infect 1995;31:67–71.
30. Jeena P, Thompson E, Nchabeleng M, Sturm A. Emergence of multi-drug-resistant Acinetobacter anitratus species in neonatal and paediatric intensive care units in a developing country: concern about antimicrobial policies. Ann Trop Paediatr 1999;19:318–321.
31. Aubekefis H, Daoud AS, Mesmar M, Obeidat A. Nosocomial neonatal septic arthritis. Eur J Pediatr 1996;155:102–105.
32. Fridkin SK, Kaufman D, Edwards JR, Shetty S, Horan T. Changing incidence of Candida bloodstream infections among NICU patients in the United States: 1995–2004. Pediatrics 2006;117:1680–1687.
33. Arora U, Jaitwani J. Acinetobacter spp. — an emerging pathogen in neonatal septicemia in Amritsar. Indian J Med Microbiol 2006;24:81.
34. Amon-Tanoh-Dick F, Lasme E, N’Gbesso RD, N’Goan-Domoua AM, Akauffou-Adja E, Diekouadio FK. Pleuropulmonary staphylococcal infection in newborn infants. Sante 1998;8:307–309.
35. Coban A, Ince Z, Ucelr R, Ozbenecli A, Can G. Neonatal suppurative parotitis: a vanishing disease! Eur J Pediatr 1993;152:1004–1005.
36. Shah A, Lagvankar S. Cutaneous mucormycosis in children. Indian Pediatr 2006;43:167–170.
37. Fox LM, Wingert S, Ahmed A, et al. Neonatal babesiosis: case report and review of the literature. Pediatr Infect Dis J 2006;25:169–173.
38. Salamati P, Rahbarimanehes AA, Yunesian M, Naseri M. Neonatal nosocomial infections in Bahrami Children Hospital. Indian J Pediatr 2006;73:197–200.
39. Burgner D, Dalton D, Hanlon M, Wong M, Kakakis A, Isaacs D. Repeated prevalence surveys of paediatric hospital-acquired infection. J Hosp Infect 1996;34:163–170.
40. Gaynes RP, Edwards JR, Jarvis WR, Culver DH, Tolson JS, Martone WJ. Nosocomial infections among neonates in high-risk nurseries in the United States. National Nosocomial Infections Surveillance System. Pediatrics 1996;98 (3 Pt 1):357–361.
41. Joshi SG, Ghole VS, Niphadkar KB. Neonatal Gram-negative bacteremia. Indian J Pediatr 2000;67:27–32.
42. Cox RA, Rao P, Brandon-Cox C. The use of palivizumab monoclonal antibody to control an outbreak of respiratory syncytial virus infection in a special care baby unit. J Hosp Infect 2001;48:186–192.
43. Berner R, Schumacher RF, Hameister S, Forster J. Occurrence and impact of community-acquired and nosocomial rotavirus infections — a hospital-based study over 10 y. Acta Paediatr Suppl 1999;88:48–52.
44. Jeong I, Jeong J, Choi EO. Epidemiological characteristics of nosocomial infection in a newborn intensive care unit (NICU), South Korea. BMC Infect Dis 2006;6:103.
45. Boo NY, Wong YH, Lim VK. Pattern of neonatal septicemia in a Malaysian maternity hospital. Med J Malaysia 1989;44:189–193.
46. Agarwal J, Bansal S, Malik GK, Jain A. Trends in neonatal septicemia: emergence of non-albicans Candida. Indian Pediatr 2004;41:712–715.
47. Boo NY, Chor CY. Six year trend of newborn septicaemia in a large Malaysian maternity hospital. J Paediatr Child Health 1994;30:23–27.
48. Boo N. Outcome of very low birthweight neonates in a developing country: experience from a large Malaysian maternity hospital. Singapore Med J 1992;33:33–37.
49. Barton L, Hodgman JE, Pavlova Z. Causes of death in the extremely low birth weight infant. Pediatrics 1999;103:446–451.
50. Wojcik-Zygadlo A, Suchanska D, Barlan L, et al. Evaluation of bacteriological research data and laboratory symptoms of infection in the diagnosis of congenital and acquired infections. Ginekol Pol 1998;69:109–114.
51. Washburn TC, Medearis Jr DN, Childs B. Sex differences in susceptibility to infections. Pediatrics 1965;35:57–64.
52. Fodha I, Landolsi N, Vabret A, Sboui H, Trabelsi A, Freymuth F. Epidemiology and clinical presentation of respiratory syncytial virus infection in a Tunisian neonatal unit from 2000 to 2002. Ann Trop Paediatr 2004;24:219–225.
53. Salian L. Risk factors for hospital-acquired infections in the neonatal intensive care unit. Semin Perinatol 2002;26:315–321.
54. Gallagher PG. Enterobacter bacteremia in pediatric patients. Rev Infect Dis 1990;12:808–812.
55. Shannon K, Fung K, Stapleton P, Anthony R, Power E, French G. A hospital outbreak of extended-spectrum beta-lactamase-producing Klebsiella pneumoniae investigated by RAPD typing and analysis of the genetics and mechanisms of resistance. J Hosp Infect 1998;39:291–300.
56. Apostolopoulos E, Lambridou M, Nikoloudi P, Pavlidou A. The relationship between pediatric risk of mortality (PRISM) score and nosocomial infections in neonatal intensive care unit. JCSU Nurs Web J 2006;23:1–6.
57. Ramachandran M, Vij A, Kumar R, et al. Lack of maternal antibodies to P serotypes may predispose neonates to infections with unusual rotavirus strains. Clin Diagn Lab Immunol 1998;5:527–530.
58. Jang TN, Fung CP, Yang TL, Shen SH, Huang CS, Lee SH. Use of pulsed-field gel electrophoresis to investigate an outbreak of Serratia marcescens infection in a neonatal intensive care unit. J Hosp Infect 2001;48:13–19.
59. Beers LM, Burke TL, Martin DB. Shigellosis occurring in newborn nursery staff. Infect Control Hosp Epidemiol 1989;10:147–149.
60. Smydman DR, Greer C, Meissner HC, McIntosh K. Prevention of nosocomial transmission of respiratory syncytial virus in a newborn nursery. Infect Control Hosp Epidemiol 1988;9:105–108.
Healthcare-associated neonatal infections

61. Waters V, Larson E, Wu F, et al. Molecular epidemiology of gram-negative bacilli from infected neonates and health care workers’ hands in neonatal intensive care units. Clin Infect Dis 2004; 38:1682–1687.

62. Gupta A. Hospital-acquired infections in the neonatal intensive care unit — Klebsiella pneumoniae. Semin Perinatol 2002; 26:340–345.

63. Gagneur A, Legrand MC, Picard B, et al. Nosocomial infections due to human coronaviruses in the newborn. Arch Pediatr 2002; 9:61–69.

64. Voss A, Melchers WJ, van den Hurk P, Bergman KA, Verweij PE, Meis JF. Fingerprinting with the polymerase chain reaction: confirmation of an Enterobacter cloacae epidemic in a neonatal intensive care unit. Immun Infect 1994; 22:214–217.

65. Bezirtzoglou E, Romond C. Nosocomial infections of ocular conjunctiva in newborns delivered by cesarean section. Ophthalmic Res 1991; 23:79–83.

66. Rowen J. Serious fungal infections in neonates and children. Abstr Intersci Conf Antimicrob Agents Chemother 2000; 40:524.

67. McDonald LC, Walker M, Carson L, et al. Outbreak of Acinetobacter spp. bloodstream infections in a nursery associated with contaminated aerosols and air conditioners. Pediatr Infect Dis J 1998; 17:716–722.

68. Lohr JA, Donowitz LG, Sadler 3rd JE. Hospital-acquired urinary tract infection. Pediatrics 1989; 83:193–199.

69. Gray JW. A 7-year study of bloodstream infections in an English children’s hospital. Eur J Pediatr 2004; 163:530–535.

70. Lohr JA, Downs SM, Dudley S, Donowitz LG. Hospital-acquired urinary tract infections in the pediatric patient: a prospective study. Pediatr Infect Dis J 1994; 13:8–12.

71. Linder N, Levit O, Klingler G, et al. Risk factors associated with candidemia in the neonatal intensive care unit: a case–control study. J Hosp Infect 2004; 57:321–324.

72. Gupta AK, Anand NK, Manmohan NK, Lamba IM, Gupta R, Srivastava L. Role of bacteriological monitoring of the hospital environment and medical equipment in a neonatal intensive care unit. J Hosp Infect 1991; 19:263–271.

73. Fryklund BA, Tullus K, Burman LG. Association between climate and Enterobacter colonization in Swedish neonatal units. Infect Control Hosp Epidemiol 1993; 14:579–582.

74. Haas J, Larson E, Ross B, See B, Saiman L. Epidemiology and diagnosis of hospital-acquired conjunctivitis among neonatal intensive care unit patients. Pediatr Infect Dis J 2005; 24:586–589.

75. Aggarwal R, Sarkar N, Deorari AK, Paul VK. Sepsis in the newborn. Indian J Pediatr 2001; 68:1143–1147.

76. Yu JL, Wu SX, Jin HQ. Study on antimicrobial susceptibility of bacteria causing neonatal infections: a 12 year study (1987–1998). Singapore Med J 2001; 42:107–110.

77. Yalaz M, Cetin H, Akisu M, Aydemir S, Tunger A, Kulturays N. Neonatal nosocomial sepsis in a level-III NICU: evaluation of the causative agents and antimicrobial susceptibilities. Turk J Pediatr 2006; 48:13–18.

78. Toledano H, Schlesinger Y, Raveh D, et al. Prospective surveillance of vancomycin-resistant enterococci in a neonatal intensive care unit. Eur J Clin Microbiol Infect Dis 2000; 19:282–287.

79. Kuruvilla KA, Thomas N, Jesudasan MV, Jana AK. Neonatal Group B Streptococcal bacteremia in India: ten years’ experience. Acta Paediatr 1999; 88:1031–1032.

80. Vinod Kumar CS, Neelagund YF. Incidence and antifungal susceptibility of Candida species in neonatal septicemia. J Commun Disord 2004; 36:182–186.

81. Levy I, Shalit I, Ashkenazi S, Klinger G, Sirota L, Linder N. Duration and outcome of persistent candidaemia in newborn infants. Mycoses 2006; 49:197–201.

82. Chong PP, Chieng DC, Low LY, et al. Recurrent candidaemia in a neonate with Hirschsprung’s disease: flucloxazole resistance and genetic relatedness of eight Candida tropicalis isolates. J Med Microbiol 2006; 55:423–428.

83. Peroniola R, Fanschi ML, Manso E, et al. Rhodotorula mucilaginosa outbreak in neonatal intensive care unit: microbiological features, clinical presentation, and analysis of related variables. Eur J Clin Microbiol Infect Dis 2006; 25:193–196.

84. Mitchell SJ, Gray J, Morgan ME, Hocking MD, Durbin GM. Nosocomial infection with Rhizopus microsorus in preterm infants: association with wooden tongue depressors. Lancet 1996; 348:441–443.

85. Verboon-Maculek MA, Krediet TG, Gerards LJ, Fleer A, van Loon TM. Clinical and epidemiologic characteristics of viral infections in a neonatal intensive care unit during a 12-year period. Pediatr Infect Dis J 2005; 24:901–904.

86. Kang JO, Kim CR. Nosocomial respiratory syncytial virus infection in a newborn nursery. J Korean Med Sci 1997; 12:489–491.

87. Gelber SE, Ratner AJ. Hospital-acquired viral pathogens in the neonatal intensive care unit. Semin Perinatol 2002; 26:346–356.

88. Diniz EM, Vieira RA, Ceccon ME, Ishida MA, Vaz FA. Incidence of respiratory viruses in preterm infants submitted to mechanical ventilation. Rev Inst Med Trop Sao Paulo 2005; 47:37–44.

89. Amir J, Wielunsy E, Zelikovic I, Varsano N, Rannan L, Reisner SH. Outbreak of respiratory syncytial virus infection in a neonatal intensive care unit. Isr J Med Sci 1984; 20:1199–1201.

90. Linhares AC, Mascarenhas JD, Gusmao RH, Gabbay YB, Fialho AM, Leite JP. Neonatal rotavirus infection in Belem, northern Brazil: nosocomial transmission of a P[6] G2 strain. J Med Virol 2002; 67:418–426.

91. Gusmao RH, Mascarenhas JD, Gabbay YB, et al. Rotavirus as a cause of nosocomial, infantile diarrhea in northern Brazil: pilot study. Mem Inst Oswaldo Cruz 1995; 90:743–749.

92. Weston PJ, Farmer K, Croxson MC, Ramirez AM. Morbidity from acquired cytomegalovirus infection in a neonatal intensive care unit. Aust Paediatr J 1989; 25:138–142.

93. Singh-Naz N, Willy M, Riggs N. Outbreak of parainfluenza virus type 3 in a neonatal nursery. Pediatr Infect Dis J 1990; 9:31–33.

94. Takami T, Sonodat S, Houjyo H, et al. Diagnosis of horizontal enterovirus infections in neonates by nested PCR and direct sequence analysis. J Hosp Infect 2000; 45:283–287.

95. Mahapatra A, Ghosh SK, Mishra S, Pattnaik D, Pattnaik K, Mohanty SK. Enterobacter cloacae: a predominant pathogen in neonatal septicaeima. Indian J Med Microbiol 2002; 20:110–112.

96. Rao S, Ali U. Systemic fungal infections in neonates. J Postgrad Med 2005; 51(Suppl. 1):S27–S29.

97. Betremieux P, Chevrier S, Quindos G, Sullivan D, Polonelli L, Guiguen C. Use of DNA fingerprinting and biotyping methods to study a Candida albicans outbreak in a neonatal intensive care unit. Pediatr Infect Dis J 1994; 13:899–905.

98. Sherrertz RJ, Gledhill KS, Hampton KD, et al. Outbreak of Candida bloodstream infections associated with retrograde medication administration in a neonatal intensive care unit. J Pediatr 1992; 120:455–461.
99. Agnihotri N, Kaitha N, Gupta V. Antimicrobial susceptibility of isolates from neonatal sepsis. Jpn J Infect Dis 2004;57:273–275.
100. Mishra A, Mishra S, Jaganath G, Mittal RK, Gupta PK, Patra DP. Acinetobacter sepsis in newborns. Indian Pediatr 1998;35:27–32.
101. Mondal GP, Raghavan M, Bhat BV, Srinivasan S. Neonatal septicemia among inborn and outborn babies in a referral hospital. Indian J Pediatr 1991;58:529–533.
102. Zaidi AK, Huskins WC, Thaver D, Bhutta ZA, Abbas Z, Goldmann DA. Hospital-acquired neonatal infections in developing countries. Lancet 2005;365:1175–1188.
103. Butt T, Ahmad RN, Usman M. Neonatal sepsis in hospital-born babies. J Coll Physicians Surg Pak 2004;14:125–126.
104. Kaushik S, Murki S, Varma S, Narang A, Chakrabarti A. Neonatal sepsis in hospital born babies. J Commun Dis 1998;30:147–152.
105. Hammerman C, Kaplan M. Probiotics and neonatal intestinal infection. Curr Opin Infect Dis 2006;19:277–282.
106. Aghai ZH, Mudduluru M, Nakhla TA, et al. Fluconazole prophylaxis in extremely low birth weight infants: association with cholestasis. J Perinatol 2006;26:550–555.
107. Manzoni P, Arisio R, Mostert M, et al. Prophylactic fluconazole is effective in preventing fungal colonization and fungal systemic infections in preterm neonates: a single-center, 6-year, retrospective cohort study. Pediatrics 2006;117:22–32.
108. Dutta S, Murki S, Varma S, Narang A, Chakrabarti A. Effects of cessation of a policy of neonatal fluconazole prophylaxis on fungal resurgence. Indian Pediatr 2005;42:1226–1230.
109. Sarvikivi E, Lyytikainen O, Soll DR, et al. Emergence of fluconazole resistance in a Candida parapsilosis strain that caused infections in a neonatal intensive care unit. J Clin Microbiol 2005;43:2729–2735.
110. Kaufman D, Boyle R, Hazen KC, Patrie JT, Robinson M, Grossman LB. Twice weekly fluconazole prophylaxis for prevention of invasive Candida infection in high-risk infants of <1000 grams birth weight. J Pediatr 2005;147:172–179.
111. Smolinski KN, Shah SS, Honig PJ, Yan AC. Neonatal cutaneous fungal infections. Curr Opin Pediatr 2005;17:486–493.
112. Stover BH, Cost KM, Hamm C, Adams G, Cook LN. Varicella exposure in a neonatal intensive care unit: case report and control measures. Am J Infect Control 1988;16:167–172.
113. Moolenaar RL, Crutcher JM, San Joaquin VH, et al. A prolonged outbreak of Pseudomonas aeruginosa in a neonatal intensive care unit: did staff fingernails play a role in disease transmission? Infect Control Hosp Epidemiol 2000;21:80–85.
114. Ayyagari A, Chander J, Narang A, et al. Outbreak of Salmonella worthington meningitis & septicaemia in a hospital at Chandigarh (north India). Indian J Med Res 1990;91:15–17.
115. Paul ML, Dwyer DE, Chow C, et al. Listeriosis – a review of eighty-four cases. Med J Aust 1994;160:489–493.
116. Goldmann DA. The bacterial flora of neonates in intensive care-monitoring and manipulation. J Hosp Infect 1988;11(Suppl A):340–351.
117. Rocha BH, Christenson JC, Pavia A, Evans RS, Gardner RM. Computerized detection of nosocomial infections in newborns. Proc Annu Symp Comput Appl Med Care 1994:684–688.
118. Isaacs D. Neonatal sepsis: the antibiotic crisis. Indian Pediatr 2005;42:9–13.
119. Villari P, Crispino M, Salvadori A, Scarcella A. Molecular epidemiology of an outbreak of Serratia marcescens in a neonatal intensive care unit. Infect Control Hosp Epidemiol 2001;22:630–634.
120. Mittal N, Nair D, Gupta N, et al. Outbreak of Acinetobacter spp septicemia in a neonatal ICU. Southeast Asian J Trop Med Pub Health 2003;34:365–366.
121. Pejaver RK, Watson AH, Mucklow ES. Neonatal cross-infection with Listeria monocytogenes. J Infect 1993;26:301–303.
122. Taneja N, Das A, Raman Rao DS, Jain N, Singh M, Sharma M. Nosocomial outbreak of diarrhoea by enterotoxigenic Escherichia coli among preterm neonates in a tertiary care hospital in India: pitfalls in healthcare. J Hosp Infect 2003;53:193–197.
123. Fok TF, Lee CH, Wong EM, et al. Risk factors for Enterobacter septicaemia in a neonatal unit: case–control study. Clin Infect Dis 1998;27:1204–1209.
124. Tresoldi AT, Padoveze MC, Trabasso P, et al. Enterobacter cloacae sepsis outbreak in a newborn unit caused by contaminated total parenteral nutrition solution. Am J Infect Control 2000;28:258–261.
125. Kadam S, Binoy S, Kanbur W, Mondkar JA, Fernandez A. Feasibility of kangaroo mother care in Mumbai. Indian J Pediatr 2005;72:35–38.