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Prevention of healthcare-associated infections in neonates: room for improvement

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SUMMARY

Infants in neonatal intensive care units (NICUs) are highly susceptible to infection due to the immaturity of their immune systems. Healthcare-associated infections (HCAIs) are associated with prolonged hospital stay, and represent a significant risk factor for neurological development problems and death. Improving HCAI control is a priority for NICUs. Many factors contribute to the occurrence of HCAIs in neonates such as poor hand hygiene, low nurse–infant ratios, environmental contamination and unnecessary use of antibiotics. Prevention is based on improving neonatal management, avoiding unnecessary use of central venous catheters, restricting use of antibiotics and H2 blockers, and introducing antifungal prophylaxis if necessary. Quality improvement interventions to reduce HCAIs in neonates seem to be the cornerstone of infection control.

Introduction

Healthcare-associated infections (HCAIs) cause substantial harm to hospitalized neonates. They have considerable health and economic consequences, including increased morbidity and mortality, prolonged length of stay (LOS) and increased medical costs.[1] In North America, it is estimated that each episode of sepsis prolongs the duration of a neonate's hospital stay by two weeks, resulting in an incremental cost of US$25,000 per episode. In a recent study of very-low-birthweight (VLBW) infants, nosocomial BSIs were found to increase hospitalization costs by 26% for infants weighing 401–750 g and by 80% for infants weighing 1251–1500 g. This study also showed that the LOS increased by four to seven days in all VLBW categories with nosocomial bloodstream infections.[2] Infants admitted to neonatal intensive care units (NICUs) are at high risk of HCAIs. They are exposed to specific and non-specific risk factors that increase the risk of bacterial and fungal sepsis, including the frequent use of broad-spectrum antimicrobial drugs, parenteral nutrition, acid inhibitors and steroids, as well as the systematic and long-term use of invasive devices such as central venous catheters (CVCs) and endotracheal tubes.[3] Preterm neonates in NICUs are at greater risk of infection due to low birth weight and intestinal disorders with proliferation of a pathogenic microflora. Moreover, nursing in incubators may delay or impair normal intestinal colonization. Neonates are more susceptible to infection because they lack an effective skin barrier, and

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have immature or ineffective immune systems, allowing invasion by many organisms from various colonized sites.[4,5]

Epidemiology

In 1999, the Pediatric Prevention Network national point prevalence survey in the USA found that 11.4% of infants in NICUs had an HCAI.[6] The most common HCAIs in this survey were BSIs (53% of HCAIs, overall prevalence 7.4%) and respiratory infections (13% of HCAIs, prevalence 1.8%). Pneumonia rates reported by others show considerable variation (7–32% of HCAIs), perhaps reflecting differences in the definitions used. Gram-positive pathogens account for up to 70% of cases of neonatal sepsis, with sepsis due to Gram-negative organisms accounting for 15–20% of infections. A study conducted between 2006 and 2008 reported the frequency of pathogens causing BSIs [coagulase-negative staphylococci (CoNS), 28%; *Staphylococcus aureus*, 19%; *Candida* spp., 13%] and the frequency of pathogens causing ventilator-associated pneumonia (VAP; *Pseudomonas aeruginosa*, 16%; *S. aureus*, 15%; *Klebsiella* spp., 14%).[7]

CoNS are the main pathogens involved in late-onset neonatal sepsis.[8] Within the first week of life, neonates are colonized rapidly by micro-organisms from the hospital environment.[9] During this period, the risk of CoNS infection increases substantially with the use of CVCs, mechanical ventilation, parenteral nutrition, and exposure to other invasive skin or mucosa-breaching procedures.[10] CoNS are common inhabitants of the skin and mucous membranes. Although a small proportion of neonates acquire CoNS by vertical transmission, acquisition is primarily horizontal by cross-transmission.[11] Consequently, infants admitted to a hospital acquire most of their micro-organisms from the hospital environment, their parents and staff.[12] Transmission via the hands of hospital staff can lead to endemic strains circulating for extended periods. As CoNS are ubiquitous skin commensal bacteria, it has been assumed that colonization of the skin and of indwelling catheters are important sources of sepsis.[13] However, recent studies have suggested that epithelial loci other than the skin, such as the nares, may be important access points of infection.[13] Antibiotic resistance in skin-residing strains has been found to be low at birth, but increases rapidly during the first week of hospitalization.[14] Therefore, selective pressure as a result of perinatal antibiotic exposure is a major factor influencing the spectrum and antibiotic resistance pattern of micro-organisms isolated from neonates.

Central-line-associated bloodstream infection

BSIs are the most common HCAIs in NICUs. BSIs are the result of interaction of several factors related to clinical care practices and characteristics of the patient population.[15] The presence of a CVC is a major risk factor for BSI. The 1999 prevalence survey in the USA found that infants with central intravascular catheters had a birthweight-adjusted relative risk of 3.8 [95% confidence interval (CI) 2.32–6.26, $P<0.001$].[6] CoNS are responsible for 50% of catheter-related infections. Interpretation of a positive blood culture is difficult as CoNS are skin commensals. The diagnosis is usually uncertain due to the non-specific signs of sepsis in this population and the definition of central-line-associated bloodstream infection (CLABSI) used in neonates. The diagnosis is often based on a single positive blood culture and clinical signs, despite the fact that many experts recommend obtaining both central line and peripheral blood cultures. A recent systematic review found significant variability in the reporting of BSI and CLABSI rates in NICUs, and confirmed that CLABSI rates are more challenging to collect.[16] As such, it may be more appropriate to use BSI rates to monitor HCAIs in some NICU settings.

Central line infections are generally a result of poor insertion technique, or failures in the hygiene protocol at the time of catheter placement and during ongoing care at the catheter site. Data suggest that the hub is the common source of contamination and subsequent infection.[17] The risk of CLABSI is related to the duration of catheter use and the frequency of catheter manipulation.[18] Many strategies have been developed in adults to prevent and reduce these HCAIs by using care bundles.[19] Reducing CLABSI should be based on implementation of clinical practice guidelines for the insertion and maintenance of catheters. Improvement consists of five care steps: maximal barrier precautions upon insertion; chlorhexidine skin antisepsis; optimal catheter site selection; optimal catheter site selection; and daily review of the need for the line, with prompt removal of unnecessary lines.[20] Several institutions have published the results of multi-faceted interventions to reduce CLABSI rates. A NICU centre conducted an educational programme aimed at reinforcing hand hygiene, and developed and implemented a checklist for care of the catheter hub. This led to a decrease in the CLABSI rate from 23 to 12 infections per 1000 catheter-days [odds ratio (OR) 0.33; 95% CI 0.20–0.90], and a decrease in the umbilical CLABSI rate from 15 to 5 infections per 1000 catheter-days (OR 0.47; 95% CI 0.17–0.91).[21] A recent literature review[20] showed that bundle implementations are effective for the reduction of CLABSI in NICUs.

Healthcare-associated pneumonia

Healthcare-associated pneumonia (HAP) represents 6.8–32.3% of HCAIs in NICUs, and is the second most common hospital-acquired infection in critically ill neonates.[22] Rates of VAP vary between 0.7 and 2.2 per 1000 ventilator-days.[23] However, as for CLABSI, rates varied between NICUs depending on birth weight and gestational age. Indeed, the risk of VAP is significantly higher below 28 weeks of gestation. Many risk factors for the development of HAP in NICU patients are similar to those identified in adult patients, such as prolonged duration of mechanical ventilation, severe underlying cardiopulmonary disease and previous thoraco-abdominal surgery.[23] Most bacterial healthcare-associated lower respiratory tract infections occur due to aspiration of bacteria from the oropharynx or the gastrointestinal tract. Uncuffed endotracheal tubes facilitate access of micro-organisms to the lower respiratory tract. Neonates with bronchopulmonary dysplasia and those who have impaired swallowing mechanisms are at increased risk of aspiration.[24]

Preventive proposed interventions include early extubation strategies and switching to non-invasive respiratory support. General concepts of prevention include: staff education and training; microbiological surveillance; prevention of cross-transmission (improving hand hygiene); and early removal of mechanical ventilation. In adult populations, a bundle including various steps for ventilator care has been developed successfully[25]: hand hygiene and compliance with use of gloves and gowns; elevation of the head-end of the bed by 30–40°;

maintenance of tracheal cuff pressure; avoidance of gastric overdistension; use of orogastric tubes; good oral hygiene; and elimination of non-essential tracheal suction. Compliance with all of these measures seems to be correlated with a decrease in the incidence of VAP.[25] Unlike in the adult population, no studies on VAP bundles in neonates have been published in the last 10 years. However, a recent study suggested that tracheal colonization by oropharyngeal bacteria was less common among neonates with mechanical ventilation when they are placed in a lateral position compared with a supine position.[26] Moreover, keeping the endotracheal tube and the ventilator circuit in a horizontal position may reduce tracking of oropharyngeal secretions into the lower respiratory tract.[27] The lateral position is also associated with reduced aspiration of gastric secretions into the trachea. As such, use of a non-supine position may reduce the risk of VAP.

Invasive fungal infections: candidaemia

Invasive fungal infections (IFIs) represent a leading cause of sepsis in VLBW infants, and result in high rates of morbidity and mortality.[28] IFIs are the third leading cause of late-onset sepsis in VLBW infants. The estimated incidence of IFIs is 1.6–3.0% in VLBW infants and up to 15–20% in extremely-low-birthweight infants. Previous mucosal and skin colonization are the main risk factors for IFIs. Neonatal colonization with *Candida* spp. is secondary to either maternal transmission or nosocomial acquisition via healthcare workers' hands in the NICU.[29] *Candida albicans* is the most prevalent fungal pathogen in neonatal disease. Recently, the prevalence rates of *Candida parapsilosis* and *Candida glabrata* infections have also increased. Several risk factors are associated with IFIs: very low birth weight; use of central lines; intubation; parenteral nutrition; broad-spectrum antibiotic administration; prolonged hospitalization; abdominal surgery; exposure to H2 blockers; and previous colonization.[30]

Colonization is the first step in the development of infection. Colonization with *Candida* spp. seems to be common in NICUs. Approximately 50% of the infants admitted to NICUs may be colonized by the end of the first week of life, and this increases to 64% by 4 weeks of age.[31] Moreover, 4.8–10.0% of neonates carry a strain of *Candida* on admission.[32] One-third of colonized neonates develop an IFI during their hospitalization.

Prevention is based on fluconazole prophylaxis. Several studies have suggested that fluconazole prophylaxis is effective.[33] A recent Cochrane meta-analysis included randomized controlled trials and quasi-randomized controlled trials that compared the effect of prophylactic systemic antifungal therapy with placebo, no drug, or another antifungal agent or dose regimen in VLBW infants.[34] This meta-analysis suggested that prophylactic systemic antifungal therapy reduces the incidence of IFIs in VLBW infants. However, this finding should be interpreted and applied with caution as the incidence of IFIs was very high in the control groups of most of the included trials. This meta-analysis did not demonstrate any significant effect on mortality.

Skin and soft tissue infections

Skin and soft tissue infections are commonly observed in NICUs as neonates have fragile skin that is easily traumatized. Cellulitis, abscesses and skin abrasion are frequently noted at sites of percutaneous puncture, in the nappy area or bandage area, and at surgical incision sites.[1] *S. aureus* is the most common micro-organism responsible for skin and soft tissue infections in NICUs.

Miscellaneous

Viral infections

The great majority of published articles have focused on bacterial and fungal infections. Neonates are also exposed to viral infection although this is largely unexplored. A recent prospective study was conducted over one year to determine the frequency of respiratory viral infections among infants who were evaluated for late-onset sepsis in NICUs at Parkland Memorial Hospital, Dallas, TX, USA.[35] During the 13-month study, eight (6%) of 135 cases of sepsis in 100 infants were positive for respiratory viruses by polymerase chain reaction (PCR) (two for enterovirus/rhinovirus, two for rhinovirus, two for coronaviruses and two for parainfluenza-3 virus). Bennett *et al.* conducted a prospective survey using multiplex PCR testing to detect respiratory viruses among infants in two NICUs over a one-year period, and found that 52% of infants aged <33 weeks of gestation tested positively for respiratory virus at least once during their birth hospitalization.[36] Viruses detected were parainfluenza virus, respiratory syncytial virus, enterovirus/rhinovirus and influenza B.

Many factors contribute to viral nosocomial infection in NICUs, as neonates are in contact not only with healthcare workers, but also with their families, sometimes including brothers and sisters. The most frequently reported viruses include rotavirus, respiratory syncytial virus, enterovirus, influenza and adenovirus. Controlling outbreaks usually require improved hand hygiene, patient screening, use of barrier precautions (gown, gloves, mask), isolation and cohorting with dedicated staff when the situation is not controlled. A recent study analysed the worldwide database of healthcare-associated outbreaks, and identified 44 neonatal viral outbreaks in NICUs.[37] Multiple measures were generally implemented to contain outbreaks, such as improving hand hygiene, use of protective clothing, systematic screening for colonization, and isolation or cohorting of infected neonates.[37]

Incubators and toys

Neonates are exposed to a number of fomites during their hospital stay, including toys and incubators. During a three-day period in a longitudinal prospective study, Raginel *et al.* observed every neonate placed in a single incubator.[38] Seventy-six percent of incubators contained at least one item that was not strictly required for nursing procedures. This study analysed 33 toys; 24 (73%) scored the maximum score for fluffiness (4 out of 4), and only 10 had labels showing cleaning advice from the manufacturers. Without any records about the cleaning and disinfection of toys brought into hospital, the authors observed that the parents had been given varied advice about how to clean the toys at home before putting them in the incubator. In particular, two of the soft toys sampled were found to be contaminated with *Pseudomonas oryzihabitans*. In another study conducted in Belgium, 23% of the swabbed toys

were found to be contaminated with various pathogens, and 9% were still contaminated despite washing at 60°C.[39]

Although there is little evidence that bacteria found on toys are a direct cause of infection in neonates, Hanrahan and Lofgren found that eliminating toys in the NICU decreased nosocomial infection rates from 4.60 to 1.99 per 1000 patient-days over a six-month period.[40]

From the authors' personal experience from Necker University Hospital, Paris (unpublished data), incubators can be the source of colonization and, in rare cases, of infection by environmental pathogens. Various case reports have described BSIs or cutaneous infections in neonates due to *Ralstonia pickettii*[41] or *Aspergillus fumigatus*.[42] The same organisms were detected in samples from the neonates and the humidity chambers, suggesting that the incubator environment may be a source of infection in NICUs.

Necrotizing enterocolitis

Necrotizing enterocolitis is one of the most severe gastrointestinal diseases in preterm neonates. Its pathogenesis is still poorly understood, but risk factors include ischaemia, altered gut microbiota, immaturity and type of enteral feeding. Presumably initial antibiotics may alter the gut microbiota, and reducing the overall antibiotic exposure of infants may reduce the risk of necrotizing enterocolitis.[43]

Strategies for the prevention of HCAIs in neonates

The lower the weight and gestational age at birth, the higher the risk of infection. Improved survival of VLBW and premature infants has led to the emergence of a population that is highly susceptible to infection. Many factors are involved in the development of HCAIs in neonates, such as immunological immaturity, frequent use of invasive procedures and prolonged hospitalization. Several infection prevention strategies have been in place for decades and are summarized below.[44]

- Improving hand hygiene is one of the most important interventions and should be a primary goal of any NICU. Successful interventions include education, monitoring, performance feedback, reminders and motivation of healthcare workers.[45]
- Prevention of CVC infection is based firstly on reducing the duration of catheterization and avoiding unnecessary use of catheters. Precautions during insertion and management of catheters are also crucial.
- Unnecessary and prolonged empirical broad-spectrum antibiotic therapy selects resistant bacteria and increases the risk of invasive fungal infections. Developing appropriate strategies to limit the use of antibiotics is the most effective way to reduce nosocomial infections due to multi-drug-resistant organisms.[46]
- Successful management and prevention of outbreaks requires sufficient facilities for cohorting colonized and infected infants. The spread of multi-drug-resistant organisms is exacerbated by inadequate spacing between cots, high occupancy rates and low nurse–infant ratios. Optimal staffing ratios for neonatal nurses appear to reduce HCAIs and mortality in neonates.[47] As environmental contamination is an important reservoir of antibiotic-selected organisms, it seems important to reduce environmental contamination by using equipment dedicated to each infant and enhancing routine cleaning.[48]

Conclusions

Neonates represent a specific population with a high risk of HCAIs. Host factors such as preterm and low birth weight, immaturity of the immune system, numerous invasive procedures, need for antimicrobial treatment, and frequent contacts with parents and healthcare workers in a hospital environment contribute to this risk. Bacterial, viral and fungal agents are responsible for HCAIs, but CLABSIs caused by CoNS remain the most common infection. Strategies to reduce HCAIs in NICUs should be based on specific bundles of care, as in adults, including improving hand hygiene, avoiding unnecessary use of catheters, appropriate use of antiseptics and avoiding unnecessary antibiotic therapy. These bundles need to be evaluated in the NICU population using quasi-experimental or randomized studies.

Conflict of interest statement

None declared.

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References

1. Polin RA, Denson S, Brady MT, Committee on Fetus and Newborn; Committee on Infectious Diseases. Epidemiology and diagnosis of health care-associated infections in the NICU. *Pediatrics* 2012;**129**:1104–1109.
2. Payne NR, Carpenter JH, Badger GJ, Horbar JD, Rogowski J. Marginal increase in cost and excess length of stay associated with nosocomial bloodstream infections in surviving very low birth weight infants. *Pediatrics* 2004;**114**:348–355.
3. Manzoni P, De Luca D, Stronati M, *et al*. Prevention of nosocomial infections in neonatal intensive care units. *Am J Perinatol* 2013;**30**:81–88.
4. Gras-Le Guen C, Lepelletier D, Debillon T, *et al*. Contamination of a milk bank pasteuriser causing a *Pseudomonas aeruginosa* outbreak in a neonatal intensive care unit. *Arch Dis Child Fetal Neonatal Ed* 2003;**88**:434–435.
5. Gras-Le Guen C, Fournier S, Andre-Richet B, *et al*. Almond oil implicated in a *Staphylococcus capitis* outbreak in a neonatal intensive care unit. *J Perinatol* 2007;**27**:713–717.
6. Sohn AH, Garrett DO, Sinkowitz-Cochran RL, *et al.*, Pediatric Prevention Network. Prevalence of nosocomial infections in neonatal intensive care unit patients: results from the first national point-prevalence survey. *J Pediatr* 2001;**139**:821–827.
7. Graham 3rd PL, Begg MD, Larson E, Della-Latta P, Allen A, Saiman L. Risk factors for late onset gram-negative sepsis in low birth weight infants hospitalized in the neonatal intensive care unit. *Pediatr Infect Dis J* 2006;**25**:113–117.
8. Jean-Baptiste N, Benjamin Jr DK, Cohen-Wolkowiez M, *et al*. Coagulase-negative staphylococcal infections in the neonatal

intensive care unit. *Infect Control Hosp Epidemiol* 2011;**32**:679–686.
9. Brady MT. Health care-associated infections in the neonatal intensive care unit. *Am J Infect Control* 2005;**33**:268–275.
10. Healy CM, Baker CJ, Palazzi DL, Campbell JR, Edwards MS. Distinguishing true coagulase-negative staphylococcus infections from contaminants in the neonatal intensive care unit. *J Perinatol* 2013;**33**:52–58.
11. Hira V, Sluijter M, Goessens WH, *et al*. Coagulase-negative staphylococcal skin carriage among neonatal intensive care unit personnel: from population to infection. *J Clin Microbiol* 2010;**48**:3876–3881.
12. Milisavljevic V, Wu F, Cimmotti J, *et al*. Genetic relatedness of *Staphylococcus epidermidis* from infected infants and staff in the neonatal intensive care unit. *Am J Infect Control* 2005;**33**:341–347.
13. Costa SF, Miceli MH, Anaissie EJ. Mucosa or skin as source of coagulase-negative staphylococcal bacteraemia? *Lancet Infect Dis* 2004;**4**:278–286.
14. Hira V, Kornelisse RF, Sluijter M, *et al*. Colonization dynamics of antibiotic-resistant coagulase-negative staphylococci in neonates. *J Clin Microbiol* 2013;**51**:595–597.
15. Holmes A, Doré CJ, Saraswatula A, *et al*. Risk factors and recommendations for rate stratification for surveillance of neonatal healthcare-associated bloodstream infection. *J Hosp Infect* 2008;**68**:66–72.
16. Folgori L, Bielicki J, Sharland M. A systematic review of strategies for reporting of neonatal hospital-acquired bloodstream infections. *Arch Dis Child Fetal Neonatal Ed* 2013;**98**: F518–F523.
17. Liñares J, Sitges-Serra A, Garau J, Pérez JL, Martín R. Pathogenesis of catheter sepsis: a prospective study with quantitative and semiquantitative cultures of catheter hub and segments. *J Clin Microbiol* 1985;**21**:357–360.
18. Mahieu LM, De Muynck AO, Ieven MM, De Dooy JJ, Goossens HJ, Van Reempts PJ. Risk factors for central vascular catheter-associated bloodstream infections among patients in a neonatal intensive care unit. *J Hosp Infect* 2001;**48**:108–116.
19. Pronovost P, Needham D, Berenholtz S, *et al*. An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med* 2006;**355**:2725–2732. Erratum in: *N Engl J Med* 2007;**356**:2660.
20. Smulders CA, van Gestel JP, Bos AP. Are central line bundles and ventilator bundles effective in critically ill neonates and children? *Intensive Care Med* 2013;**39**:1352–1358.
21. Sannoh S, Clones B, Munoz J, Montecalvo M, Parvez B. A multimodal approach to central venous catheter hub care can decrease catheter-related bloodstream infection. *Am J Infect Control* 2010;**38**:424–429.
22. Hooven TA, Polin RA. Healthcare-associated infections in the hospitalized neonate: a review. *Early Hum Dev* 2014;**90**(Suppl. 1):S4–S6.
23. Foglia E, Meier MD, Elward A. Ventilator-associated pneumonia in neonatal and pediatric intensive care unit patients. *Clin Microbiol Rev* 2007;**20**:409–425.
24. Tan B, Zhang F, Zhang X, *et al*. Risk factors for ventilator-associated pneumonia in the neonatal intensive care unit: a meta-analysis of observational studies. *Eur J Pediatr* 2014;**173**:427–434.
25. Bouadma L, Deslandes E, Lolom I, *et al*. Long-term impact of a multifaceted prevention program on ventilator-associated pneumonia in a medical intensive care unit. *Clin Infect Dis* 2010;**51**:1115–1122.
26. Torres A, Serra-Batlles J, Ros E, *et al*. Pulmonary aspiration of gastric contents in patients receiving mechanical ventilation: the effect of body position. *Ann Intern Med* 1992;**116**:540–543.
27. Aly H, Badawy M, El-Kholy A, Nabil R, Mohamed A. Randomized, controlled trial on tracheal colonization of ventilated infants: can gravity prevent ventilator-associated pneumonia? *Pediatrics* 2008;**122**:770–774.
28. Kaufman DA, Manzoni P. Strategies to prevent invasive candidal infection in extremely preterm infants. *Clin Perinatol* 2010;**37**:611–628.
29. Chapman RL. Prevention and treatment of candida infections in neonates. *Semin Perinatol* 2007;**31**:39–46.
30. Benjamin Jr DK, Stoll BJ, Fanaroff AA, *et al.*, National Institute of Child Health and Human Development Neonatal Research Network. Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months. *Pediatrics* 2006;**117**:84–92.
31. Baley JE, Kliegman RM, Boxerbaum B, Fanaroff AA. Fungal colonization in the very low birth weight infant. *Pediatrics* 1986;**78**:225–232.
32. Smith PB, Steinbach WJ, Cotten CM, *et al*. Caspofungin for the treatment of azole resistant candidemia in a premature infant. *J Perinatol* 2007;**27**:127–129.
33. Leibovitz E. Strategies for the prevention of neonatal candidiasis. *Pediatr Neonatol* 2012;**53**:83–89.
34. Austin NC, Darlow B. Prophylactic oral antifungal agents to prevent systemic candida infection in preterm infants. *Cochrane Database Syst Rev* 2004;(1):CD003478.
35. Ronchi A, Michelow IC, Chapin KC, *et al*. Viral respiratory tract infections in the neonatal intensive care unit: the VIRIoN-I study. *J Pediatr* 2014;**165**:690–696.
36. Bennett NJ, Tabarani CM, Bartholoma NM, *et al*. Unrecognized viral respiratory tract infections in premature infants during their birth hospitalization: a prospective surveillance study in two neonatal intensive care units. *J Pediatr* 2012;**161**:814–818.
37. Civardi E, Tzialla C, Baldanti F, Strocchio L, Manzoni P, Stronati M. Viral outbreaks in neonatal intensive care units: what we do not know. *Am J Infect Control* 2013;**41**:854–856.
38. Raginel T, Bigoin-Dupont M, Aguelon V, Fines-Guyon M, Guillemin MG. Audit 'Toys and incubators in neonatology'. *Arch Pediatr* 2009;**16**:1202–1207.
39. Naesens R, Jeurissen A, Vandeputte C, Cossey V, Schuermans A. Washing toys in a neonatal intensive care unit decreases bacterial load of potential pathogens. *J Hosp Infect* 2009;**71**:197–198.
40. Hanrahan KS, Lofgren M. Evidence-based practice: examining the risk of toys in the microenvironment of infants in the neonatal intensive care unit. *Adv Neonatal Care* 2004;**4**:184–201.
41. Adiloğlu AK, Ayata A, Sirin C, Yöndem C, Okutan H. Case report: nosocomial *Ralstonia pickettii* infection in neonatal intensive care unit. *Mikrobiyol Bul* 2004;**38**:257–260.
42. Etienne KA, Subudhi CP, Chadwick PR, *et al*. Investigation of a cluster of cutaneous aspergillosis in a neonatal intensive care unit. *J Hosp Infect* 2011;**79**:344–348.
43. Kim JH. Necrotizing enterocolitis: the road to zero. *Semin Fetal Neonatal Med* 2014;**19**:39–44.
44. Borghesi A, Stronati M. Strategies for the prevention of hospital-acquired infections in the neonatal intensive care unit. *J Hosp Infect* 2008;**68**:293–300.
45. Pessoa-Silva CL, Hugonnet S, Pfister R, *et al*. Reduction of health care associated infection risk in neonates by successful hand hygiene promotion. *Pediatrics* 2007;**120**:e382–e390.
46. Cantey JB, Patel SJ. Antimicrobial stewardship in the NICU. *Infect Dis Clin N Am* 2014;**28**:247–261.
47. Anthony M, Bedford-Russell A, Cooper T, *et al*. Managing and preventing outbreaks of Gram-negative infections in UK neonatal units. *Arch Dis Child Fetal Neonatal Ed* 2013;**98**:F549–F553.
48. Sherenian M, Profit J, Schmidt B, *et al*. Nurse-to-patient ratios and neonatal outcomes: a brief systematic review. *Neonatology* 2013;**104**:179–183.