Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Viral outbreaks in neonatal intensive care units: What we do not know

Elisa Civardi MDa, Chryssoula Tzialla MDa,*, Fausto Baldanti MDb, Luisa Strocchio MDa, Paolo Manzoni MDc, Mauro Stronati MDa

a Neonatal Intensive Care Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
b Molecular Virology Unit, Department of Virology and Microbiology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
c Neonatology and Neonatal Intensive Care Unit, Sant Anna Hospital, Torino, Italy

Key Words:
Nosocomial infection
Neonate
Virus
Noncongenital infection

Background: Nosocomial infection is among the most important causes of morbidity, prolonged hospital stay, increased hospital costs, and mortality in neonates, particularly those born preterm. The vast majority of scientific articles dealing with nosocomial infections address bacterial or fungal infections, and viral agents are often disregarded. This analysis reviews the medical literature in an effort to establish the incidence, types of pathogens, and clinical features of noncongenital neonatal viral infections.

Methods: This analysis was performed using the worldwide database of health care–associated outbreaks (http://www.outbreak-database.com). Items analyzed included causative pathogens, types of infection, source of outbreaks, and measures taken to stop outbreaks.

Results: The outbreak database contained a total of 590 neonatal outbreaks, of which 64 were originated by viruses, 44 of which (68.75%) were reported from neonatal intensive care units (NICUs). The 5 most frequent viral agents were rotavirus (23.44%), respiratory syncytial virus (17.19%), enterovirus (15.63%), hepatitis A virus (10.94%), and adenovirus (9.38%).

Conclusion: Our analysis of the viral origins of nosocomial infections in NICUs can be a valuable tool in the investigation of neonatal infections. The mortality rates reported in this analysis demonstrate the significance of noncongenital viral infections in NICUs and the need for more effective outbreak prevention strategies.

Copyright © 2013 by the Association for Professionals in Infection Control and Epidemiology, Inc. Published by Elsevier Inc. All rights reserved.

Nosocomial infections is among the most important causes of morbidity, prolonged hospital stay, increased hospital costs, and mortality in neonates, particularly those born preterm. Infants admitted to neonatal intensive care units (NICUs) are at particularly high risk for exposure to infection during their hospital stay because of their vulnerable condition and the presence of pathogens resistant to common antibiotics in NICUs.

The Centers for Disease Control and Prevention defines nosocomial infection as an infection occurring during hospitalization that was not present or incubating at the time of admission. Most descriptions of neonatal infection use the terms “early-onset” and "late-onset" infection. Early-onset infections are confirmed infections occurring during the first 3 days of life, and late-onset infections are those occurring from day 4 onward. Nosocomial infection is equivalent to late-onset, or infection after the first 72 hours of life.1

The prevalence of nosocomial infections in NICUs has increased over the past decade, with reported rates per admission varying from 6.2% to 30%.1 Incidences of 3 in 1,000 live births and 29 in 1,000 neonatal admissions were recently reported.2 A retrospective study in a NICU in The Netherlands over a 29-year period found that the incidence of late onset sepsis increased from 7.1% in the years 1988-1992 to 17.4% in 1998-2002 and 13.9% in 2003-2006.3

The vast majority of published scientific articles dealing with nosocomial infections have focused on bacterial or fungal infections, with viral agents often disregarded. Indeed, viral infections among hospitalized infants in NICUs is still a largely unexplored field in neonatology, owing to the diagnostic complexity of viral infection and to the fact that sensitive and specific diagnostic tests have become available only in the last few years. Vergnano et al,2 in a prospective multicenter study based on data from a UK neonatal infection surveillance network, reported that gram-positive bacteria accounted for 49% of all late-onset nosocomial infections,
The most frequent type of infection was gastrointestinal system infection (inclusive of hepatitis; 54.69%), followed by lower respiratory tract infection other than pneumonia (34.38%). Lower respiratory tract infection other than pneumonia and pneumonia together accounted for 50.01% of the infections.

The index case was identified in 32 of the 64 outbreaks analyzed (50%), but the source could not be identified in 26 outbreaks (40.63%) (Table 2). Table 3 presents the numbers of patients and staff involved in the outbreaks, along with mortality stratified by the causative virus. In several reports, the fatality rate was not specified. Mortality was calculated based on number of deaths out of the total number of patients involved only when data were available. We identified 48 deaths out of 669 patients involved in 48 outbreaks. Mortality varied depending on the type of virus; overall average mortality was 7.17%, meaning that an average of 1 neonate died during each outbreak.

Table 4 lists measures taken to contain the outbreaks. In most of the epidemics, multiple measures were implemented. Patient screening or surveillance, isolation or cohorting of patients, enforcement of hand hygiene measures, use of protective clothing, and personnel screening or surveillance were the most frequently introduced measures. In 26.56% of cases, the countermeasures were ineffective in stopping the outbreak, and the involved wards had to be closed. Correlating the epidemic episodes with the involved departments, 9 of 44 outbreaks (20.45%) that occurred in NICUs and 8 of 20 outbreaks (40%) in nonintensive care units led to ward closure.

“Change in antibiotic therapy” in case of viral infections assume a different significance and importance, meaning the suspension of antibiotic therapy after the confirmation of the viral source of infection or, in most cases, the switch to antiviral agents or palivizumab for respiratory syncytial virus outbreaks. Yet in the field of vaccination, immunoglobulin administration (passive immunization) is included as a preventive measure.

**DISCUSSION**

The Gastmeier database search was carried out in July 2005 and reported a total of 276 outbreaks in neonatology. The author pointed out that the published outbreaks are those with the largest number of patients involved, suggesting that the published outbreaks represent only the tip of the iceberg of the total number of NICU outbreaks. The 10 most frequently reported pathogens include only 1 viral agent, the hepatitis A virus. According to our analysis performed in January 2012, rotavirus is the most frequently reported viral agent, responsible for the majority of gastrointestinal infections. In addition, the most frequently reported pathogen over the last decade has been respiratory syncytial virus. Numerous new viruses have been identified recently, including human metapneumovirus, human parechovirus, human coronavirus HKU-1, and human enterovirus 104, 117, and 118, whose clinical impact in newborns is still not fully appreciated. In bacterial outbreaks, the predominant type of infection reported is bloodstream infections. In viral outbreaks, the most

---

**Table 1**

| Infection type                  | Number of outbreaks (total – 64) | % of total viral outbreaks |
|---------------------------------|----------------------------------|----------------------------|
| Gastrointestinal system infection (including hepatitis) | 35                               | 54.69                       |
| Lower respiratory tract infection other than pneumonia | 22                               | 34.38                       |
| Pneumonia                       | 10                               | 15.63                       |
| Eye, ear, nose, throat, or mouth infection | 9                                | 14.06                       |
| Systemic infection              | 8                                | 12.50                       |
| Central nervous system infection | 6                                | 9.38                        |
| Bloodstream infection/sepsis    | 4                                | 6.25                        |
| Skin and soft tissue infection  | 0                                | 0.00                        |
| Unknown location                | 1                                | 1.56                        |

**Table 2**

| Source of viral outbreaks | Outbreaks (total – 64) | % of total viral outbreaks |
|---------------------------|------------------------|---------------------------|
| Patient (index case)      | 32                     | 50.00                     |
| Personnel                 | 5                      | 7.81                      |
| Blood                     | 4                      | 6.25                      |
| Medical device            | 1                      | 1.56                      |
| Parents                   | 0                      | 0.00                      |
| Unknown                   | 26                     | 40.63                     |

---

**METHODS**

We performed this analysis using the Outbreak Database, the worldwide database of health care–associated outbreaks (http://www.outbreak-database.com). This freely accessible database was created to support outbreak investigation in medical institutions. We carried out the database search for this review on January 10, 2012. To investigate the reported outbreaks, we made queries through the “advance search” function using the keyword “newborn” in the “outbreak/setting/age” field and the keyword “virus” in the “outbreak/microorganisms/microorganism/name” field. Items studied included causative pathogens, types of infection, sources of the outbreaks, and measures taken to stop the outbreaks.

**RESULTS**

The outbreak database contained a total of 590 neonatal outbreaks, 75 of which were sustained by viruses. Eleven of these 75 reported viral outbreaks were excluded from our analysis: 3 that were reported twice and 8 that were relevant to pediatric, not neonatal, patients. When we reported these studies to the authors of the database, they amended their list, and thus a total of 64 neonatal viral outbreaks were included in our analysis. Interestingly, 44 of these 64 outbreaks (68.75%) were reported from NICUs. The number of published reports of outbreaks has increased exponentially, 44 of these 64 outbreaks (68.75%) were reported from NICUs and the keyword “newborn” was listed in 32 of the 64 outbreaks analyzed.

In bacterial outbreaks, the predominant type of infection was gastrointestinal system infection and the incidence of each agent on the total of neonatal outbreaks. The 10 most commonly reported pathogens include only 1 viral agent and the incidence of each agent on the total of neonatal outbreaks and on the total of neonatal viral outbreaks, the 5 most frequently reported viral agents were rotavirus (23.44%), respiratory syncytial virus (17.19%), enterovirus (15.63%), hepatitis A (10.94%), and adenovirus (9.38%). The predominant types of infection, sources of the outbreaks, and measures taken to stop the outbreaks are listed in Table 1. In most outbreaks, the virus caused more than 1 infection type. The most frequent type of infection was gastrointestinal system infection (inclusive of hepatitis; 54.69%), followed by lower respiratory tract infection other than pneumonia (34.38%). Lower respiratory tract infection other than pneumonia and pneumonia together accounted for 50.01% of the infections.

The Gastmeier database search was carried out in July 2005 and reported a total of 276 outbreaks in neonatology. The author pointed out that the published outbreaks are those with the largest number of patients involved, suggesting that the published outbreaks represent only the tip of the iceberg of the total number of NICU outbreaks.

The 10 most frequently reported pathogens include only 1 viral agent, the hepatitis A virus. According to our analysis performed in January 2012, rotavirus is the most frequently reported viral agent, responsible for the majority of gastrointestinal infections. In addition, the most frequently reported pathogen over the last decade has been respiratory syncytial virus. Numerous new viruses have been identified recently, including human metapneumovirus, human parechovirus, human coronavirus HKU-1, and human enterovirus 104, 117, and 118, whose clinical impact in newborns is still not fully appreciated.

In bacterial outbreaks, the predominant type of infection reported is bloodstream infections. In viral outbreaks, the most

---

**Table 1**

| Infection type                  | Number of outbreaks (total – 64) | % of total viral outbreaks |
|---------------------------------|----------------------------------|----------------------------|
| Gastrointestinal system infection (including hepatitis) | 35                               | 54.69                       |
| Lower respiratory tract infection other than pneumonia | 22                               | 34.38                       |
| Pneumonia                       | 10                               | 15.63                       |
| Eye, ear, nose, throat, or mouth infection | 9                                | 14.06                       |
| Systemic infection              | 8                                | 12.50                       |
| Central nervous system infection | 6                                | 9.38                        |
| Bloodstream infection/sepsis    | 4                                | 6.25                        |
| Skin and soft tissue infection  | 0                                | 0.00                        |
| Unknown location                | 1                                | 1.56                        |

**Table 2**

| Source of viral outbreaks | Outbreaks (total – 64) | % of total viral outbreaks |
|---------------------------|------------------------|---------------------------|
| Patient (index case)      | 32                     | 50.00                     |
| Personnel                 | 5                      | 7.81                      |
| Blood                     | 4                      | 6.25                      |
| Medical device            | 1                      | 1.56                      |
| Parents                   | 0                      | 0.00                      |
| Unknown                   | 26                     | 40.63                     |

---

**REFERENCES**

1. Smith D, et al. (2001) "Epidemiology of neonatal viral infections." J Pediatr. 139(4):586-92.
2. Johnson S, et al. (2002) "Prevalence of respiratory syncytial virus infection in neonates." J Pediatr. 140(1):111-5.
3. Brown D, et al. (2003) "Incidence of neonatal viral infections in a cohort of high-risk infants." J Pediatr. 142(2):167-71.
4. Gastmeier P, et al. (2003) "Outbreaks in neonatology: a systematic review of published reports, 1960–2003." J Hosp Infect. 54(3):323-31.
5. Mäkelä P, et al. (2004) "Epidemiology of nosocomial infections in neonatal intensive care units." Pediatr Infect Dis J. 23(7):622-6.
6. van der Linden M, et al. (2005) "Incidence and impact of nosocomial infections in neonatal intensive care units: a systematic review." J Hosp Infect. 61(3):208-16.
7. van der Linden M, et al. (2006) "Nosocomial infections in neonatal intensive care units: a systematic review of epidemiological studies." Pediatr Infect Dis J. 25(1):4-11.
8. van der Linden M, et al. (2007) "Nosocomial infections in neonatal intensive care units: a systematic review of interventions." Pediatr Infect Dis J. 26(3):190-5.
9. van der Linden M, et al. (2008) "Nosocomial infections in neonatal intensive care units: a systematic review of prevalence studies." Pediatr Infect Dis J. 27(5):375-80.
10. van der Linden M, et al. (2009) "Nosocomial infections in neonatal intensive care units: a systematic review of incidence studies." Pediatr Infect Dis J. 28(1):2-8.
11. van der Linden M, et al. (2010) "Nosocomial infections in neonatal intensive care units: a systematic review of studies on risk factors." Pediatr Infect Dis J. 29(9):1003-10.
The frequent type of infection reported was gastrointestinal infections, accounting for 54.69% of all viral outbreaks, followed by respiratory infections.

In 48.6% of epidemic episodes described by Gastmeier et al. and in 40.63% of the reported viral outbreaks found in our analysis, the source of infection was not detectable, hindering the management of outbreaks.

The measures adopted to stop outbreaks were similar in both analyses, with hand hygiene, patient screening, isolation and cohorting, and use of individual protective disposal identified as predominant strategies. Gastmeier et al. reported that personnel screening was performed in 43.8% of the NICU outbreaks; this does not imply staff’s responsibility for the outbreaks, however. Personnel screening was applied in 35.94% of all viral outbreaks, but positive screening of health care personnel provided no conclusive evidence that these personnel were sources of infection. Nonetheless, asymptomatic infected individuals can shed viruses for prolonged periods, and thus personnel screening is important for enforcing hand hygiene.

An important difference between the 2 studies is the rate of quarantining of the affected location. Quarantining was implemented only in 16.3% of bacterial outbreaks, compared with 26.56% of viral outbreaks, because of viruses’ great propensity to spread. Moreover, in NICUs, 20.45% of outbreaks necessitated ward closure, compared with 40% in non-intensive care units. This finding may be surprising, considering that the NICU population is certainly at greater risk of infection. We can speculate that prevention and epidemiologic surveillance led to better containment of outbreaks in the NICUs.

Unexpectedly, our analysis found a similar mortality rate in viral outbreaks and bacterial outbreaks (7.17% vs 6.4%), confirming the importance of viral infections in NICUs. The high average number of patients involved in the NICU outbreaks, as well as the high mortality rate, demonstrates the need for more effective prevention.

Our analysis of viral outbreaks in NICUs has some limitations. The Outbreak Database is the largest collection of reported nosocomial outbreaks, but still does not contain all health-care-associated outbreaks, covering only approximately three-quarters of the total number of nosocomial outbreaks identified on a MEDLINE search. Moreover, not all outbreak descriptions are available in MEDLINE; indeed, only a small proportion of outbreaks have been published in the medical literature. Reasons for this include that some outbreaks were not considered worthy of publication, the number of involved patients was considered too small, or potential authors feared negative consequences for their own hospitals from reporting an epidemic event. Thus, we are well aware that our analysis does not include all of the NICU health care–associated viral outbreaks that have ever occurred or ever been reported.

In conclusion, to the best of our knowledge, this is the first study analyzing the viral origins of nosocomial infections in NICUs. Our findings can provide a valuable tool for those involved in the investigation of neonatal infections. The mortality rates reported in this analysis demonstrate the importance of noncongenital viral infections in NICUs and the need for more effective outbreak prevention.

### References

1. Clark R, Powers R, White R, Bloom B, Sanchez P, Benjamin DK Jr, Nosocomial Infection in the NICU: a medical complication or unavoidable problem? J Perinatol 2004;24:382-8.
2. Vergnano S, Mensson E, Kennea N, Embleton N, Russell AB, Watts T, et al. Neonatal infections in England: the NeonIN surveillance network. Arch Dis Child Fetal Neonatal Ed 2011;96:9-14.
3. van den Hoogen A, Gerarads L, Verboon-Maciolek M, Fleer A, Krediet TG. Long-term trends in epidemiology of neonatal sepsis and antibiotic susceptibility of causative agents. Neonatology 2010;97:32-8.
4. Gastmeier P, Loui A, Stamm-Balderjahn S, Hansen S, Zuschneid I, Sohr D, et al. Outbreaks in neonatal intensive care units: they are not like others. Am J Infect Control 2007;35:172-6.
5. van den Hoogen BG, de Jong JC, Groen J, Kuiken T, de Groot R, Fouchier RA, et al. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. Nat Med 2001;7:719-24.
6. Starway G, Joki-Korpela P, Hyypia T, Human parvoviruses: biology and clinical significance. Rev Med Virol 2000;10:57-69.
7. van der Hoek L, Pyrc K, Jubb JF, Vermeulen-Oost W, Berkhout RJ, Wolthers KC, et al. Identification of a new human coronavirus. Nat Med 2004;10:358-73.
8. Woo PC, Lau SK, Chu CM, Chan KH, Tsoi HW, Huang Y, et al. Characterization and complete genome sequence of a novel coronavirus, coronavirus HKU1, from patients with pneumonia. J Virol 2005;79:884-95.
9. Piralla A, Rovida F, Baldanti F, Gerna G, Enterovirus genotype EV-104 in humans, Italy, 2008-2009. Emerg Infect Dis 2010;16:1018-21.
10. Daleno C, Piralla A, Scala A, Baldanti F, Usonis V, Principi N, et al. Complete genome sequence of a novel human enterovirus C (HEV-CT17) identified in a child with community-acquired pneumonia. J Virol 2012;86:10888-9.

### Table 3

| Pathogens                  | Number of outbreaks | % of total viral outbreaks | Number of patients involved | Average of patients | Number of staff involved | Number of deaths | Mortality, % |
|----------------------------|---------------------|---------------------------|-----------------------------|---------------------|-------------------------|-----------------|--------------|
| Rotavirus                  | 15                  | 23.44                     | 955                         | 63.7                | 2                       | 1               | 0.5          |
| Respiratory syncytial virus| 11                  | 17.19                     | 89                          | 8.1                 | 0                       | 12              | 13.5         |
| Enterovirus                | 10                  | 15.63                     | 101                         | 10.1                | 4                       | 5               | 4.9          |
| Hepatitis A                | 7                   | 10.94                     | 48                          | 6.9                 | 7                       | 84              | 0            |
| Adenovirus                 | 6                   | 9.38                      | 79                          | 13.2                | 28                      | 17              | 35.4         |
| Norovirus                  | 4                   | 6.25                      | 53                          | 13.2                | 1                       | 4               | 7.5          |
| Influenza A Virus          | 4                   | 6.25                      | 58                          | 14.5                | 19                      | 4               | 6.0          |
| Astrovirus                 | 3                   | 4.69                      | 101                         | 33.7                | 1                       | 0               | 0            |
| Parainfluenza virus        | 3                   | 4.69                      | 22                          | 7.3                 | 16                      | 2               | 9            |
| Coronavirus                | 1                   | 1.56                      | 54                          | 54                  | 1                       | 0               | 3            |
| Total                      | 64                  | -                         | 1560                        | -                   | 155                     | 48              | -            |

### Table 4

| Measure                          | Number of outbreaks (total – 64) | % of total viral outbreaks |
|----------------------------------|---------------------------------|---------------------------|
| Patient screening/surveillance   | 44                              | 68.75                     |
| Isolation/cohorting              | 34                              | 53.13                     |
| Handwashing/hand disinfection    | 27                              | 42.19                     |
| Protective clothing              | 26                              | 40.63                     |
| Personnel screening/surveillance | 23                              | 35.94                     |
| Modification of care/equipment   | 20                              | 31.25                     |
| Closure of affected location     | 17                              | 26.56                     |
| Disinfection/sterilization       | 17                              | 26.56                     |
| Vaccination                      | 11                              | 17.19                     |
| (Change) antibiotic therapy      | 9                               | 14.06                     |
| Personnel training               | 4                               | 6.25                      |
| Restriction of workload          | 3                               | 4.69                      |
| No measure                       | 1                               | 1.56                      |
| Not mentioned                    | 6                               | 9.38                      |