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Major article

Viral outbreaks in neonatal intensive care units: What we do not know

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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.

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,

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Table 1
Infection types in outbreaks

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

gram-negative bacteria for 42%, and fungi for 9%; viral agents were not investigated. Indeed, the role of nosocomial virus infections is generally neglected in epidemiologic scenarios.

The aim of the present analysis was initially to review medical literature to establish the incidence, types of pathogens, and clinical features of noncongenital neonatal viral infections. However, this goal proved not easily achievable, owing to the lack of data in the literature. In this study, we used the same database of health care–associated outbreaks used by Gastmeier et al in a 2007 study,[4] but focused our analysis on viral outbreaks in neonates.

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 over time over the last several decades, from 3 before to 14 in the 1980s and 13 in the 1990 to 34 from 2000 to the present.

Considering the number of reported outbreaks for any 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 health care–associated infections identified 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.

Table 2
Source of outbreaks

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

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[4] 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,[5] human parechovirus,[6] human coronavirus NL63,[7] human coronavirus HKU-1,[8] and human enterovirus 104, 117, and 118,[9,10] 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 3
Number of involved individuals and mortality stratified by pathogens

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	84	0	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	6.9
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	0	3	5.6
Total	64	—	1560	—	155	48	—

Table 4
Measures to stop outbreaks

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

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[4] 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,[4] 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%),[4] confirming the importance of viral infections in NICU. 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.

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