

Quantifying Prevalence and Mortality Associated with Neonatal Enteroviral Sepsis (NES) Using Inpatient Data in FDA's Sentinel System

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Background

- Neonatal enteroviral sepsis (NES) is a severe enterovirus (EV) infection in the neonate that may manifest with serious complications such as hepatic necrosis, coagulopathy, and myocarditis. Among neonates with EV-infection, and hepatic necrosis, coagulopathy and/or myocardial involvement, case-fatality rates between 0 to 83% have been reported.¹⁻³
- Currently no U.S. Food and Drug Administration (FDA) approved drug product exists for the treatment of NES, although reports indicate intravenous immune globulin (IVIG) is sometimes administered.⁴
- Limited data are available regarding the epidemiology of NES. FDA required observational data on NES prevalence and mortality rates to inform the design of future clinical trials to evaluate investigational new drugs for NES treatment.

Objective

To describe NES prevalence and mortality rates among hospitalized neonates in the U.S. FDA Sentinel System

Methods

Population

- Potential NES cases were identified using Sentinel inpatient EHR data from 7/1/2012 – 3/31/2016
- Patients aged <60 days on admission were considered eligible for inclusion. This included neonates aged 0-30 days and older infants aged 31-60 days

NES case definition criteria

- Laboratory confirmation of EV infection was not available
- Potential NES cases were identified using a combination of diagnostic code-based case definitions denoting sepsis and EV-infection, as well as hepatic necrosis, coagulopathy and myocarditis
- Case definition criteria levels were constructed based on combinations codes for EV-infection, sepsis, and one or more of the organ dysfunctions to satisfy the NES case definition criteria (Table 1)

Exclusion criterion

- Potential NES cases with greater than 2 administration dates of antibacterial, antiviral, or antifungal therapy allowing a gap of 1 day after the first administration date, identified from the inpatient pharmacy table, were excluded
- Neonates hospitalized with suspected sepsis typically receive broad antimicrobial treatments such as the aforementioned therapies. Once bacterial, fungal or herpetic infection are excluded, or if EV-infection is diagnosed, these agents are normally discontinued

Patient characteristics

- Patient demographics
 - age in days
 - sex
- Hospitalization characteristics
 - admission year
 - length of stay
 - discharge disposition
 - receipt of therapy (IVIG)

Results

- Among all eligible hospitalizations of neonates in 119 facilities during the study period (n= 842,260), 10 patients with EV-infection and sepsis were identified and of these, 7 met the stricter NES case definition criteria. Of the 7, 3 presented with EV-infection, sepsis, and coagulopathy, and 2 had EV-infection sepsis, coagulopathy, and myocarditis (Table 1 & 2).
- NES prevalence was 0.83 per 100,000 neonate inpatient stays.
- At admission, the majority (86%) of the patients with NES were <30 days old (Table 2).
- EV-infected patients with organ dysfunction had longer length of stay (LOS) (median LOS 91 days, range 46-347 days, depending on specific organ dysfunction) compared to those without organ dysfunction (median LOS 3 days, range 3-11 days).
- One NES patient received IVIG therapy (Table 2).
- No in-hospital deaths were observed among NES cases.

Table 2. Baseline characteristics associated with NES inpatient stays and all neonate inpatient stays identified at one Sentinel Data Partner from July 2012 - March 2016

	Inpatient encounters in neonates with NES according to definition 1-7, N=7	Percent inpatient encounters in neonates with NES	All inpatient encounters in neonates, N=842,260	Percent all inpatient encounters in neonates
Demographics				
Age at admission (days)				
0-30	6	86%	831,831	99%
31-60	1	14%	10,429	1%
Sex				
Female	3	43%	408,795	49%
Male	4	57%	432,581	51%
Unknown	0	0%	884	0%
Hospitalization characteristics				
Admission year				
2012	0	0%	114,574	14%
2013	4	57%	219,960	26%
2014	2	29%	226,312	27%
2015	1	14%	229,071	27%
2016	0	0%	52,343	6%
Intravenous Immunoglobulin (IVIG) treatment				
IVIG treatment during the encounter	1	14%	1482	0%

Table 1. Number of cases that met each case definition level 1-8

Case definition criteria	NES case definition criteria					No. of cases identified
	Sepsis	EV	Coagulopathy	Hepatic Necrosis	Myocarditis	
1 (Most strict)	X	X	X	X	X	0
2	X	X	X	X		0
3	X	X	X		X	2
4	X	X		X	X	0
5	X	X	X			3
6	X	X		X		1
7	X	X			X	1
8 (Least strict)	X	X				3

Conclusions

- NES, identified using diagnosis code based criteria, was rare among hospitalized neonates in this preliminary analysis, and no cases resulted in death.
- This was the first study to examine NES prevalence using inpatient data from the Sentinel System. Future work might include validation of potential NES cases with medical record review. Additional data are needed to characterize factors that might impact clinical outcomes among patients with NES to inform the design of future clinical trials.

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