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Vasoactive medications in extremely low gestational age neonates during the first postnatal week

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Abstract

Objective: The management of early hypotension in extremely low gestational age neonates (ELGANs) varies greatly between centers. The objective of this study was to provide updated data on the use of vasoactive medications in ELGANs during the first postnatal week.

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AUTHOR CONTRIBUTIONS

All authors were involved in the study design, analysis, and manuscript revision. All authors read and approved the final manuscript. Dr. Miller is the guarantor who accepts full responsibility for the work and the conduct of the study, has access to the data, and controlled the decision to publish.

LE Miller: Dr. Miller contributed to the conception and design of the study, the data interpretation, the manuscript drafting, and the critical revision of the manuscript.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

Study design: We identified ELGANs (22-27 weeks gestational age) cared for at Pediatric neonatal intensive care units from 2009-2018. We evaluated the frequency of exposure to vasoactive medications by gestational age, and compared use of vasoactive medications between 2 epochs (2009-2013 and 2014-2018).

Results: A total of 10 070/34 234 (29%) ELGANs received 1 vasoactive medication. Dopamine was the most frequently used vasoactive medication. The majority (83%) of treated ELGANs initiated therapy on postnatal day 0-1. Overall use of vasoactive medications was slightly lower in 2014-2018 than 2009-2013 (28% vs 31%, $p < 0.001$).

Conclusion: A substantial proportion of ELGANs were exposed to vasoactive medications during the first postnatal week.

INTRODUCTION

There is no clear consensus regarding the diagnosis or management of early hypotension in extremely low gestational age neonates (ELGANs). Low blood pressure (BP) is a common concern in ELGANs during the first postnatal week,^{1, 2} and it can be challenging for clinicians to differentiate normal, transitional hemodynamic changes from pathophysiologic hypotension that requires treatment. Several studies have shown that early hypotension in ELGANs is associated with both short and long-term adverse outcomes, including intraventricular hemorrhage (IVH), neurodevelopmental impairment, and death.^{1, 3, 4} These findings have led many clinicians to use medications in order to raise BP to “normal” values. Treatment strategies include volume expansion, vasoactive medications, corticosteroids, or a combination of therapies. Unfortunately, the majority of studies have not demonstrated decreased morbidity and mortality in neonates treated for hypotension.^{5, 6, 7, 8, 9} Some studies even suggest that treatment of hypotension is independently associated with harm.^{2, 5, 6, 7, 8, 10, 11, 12, 13, 14, 15}

Vasoactive medications (vasopressors and inotropes) are frequently used in the management of early hypotension in ELGANs, despite a paucity of efficacy and safety data.^{5, 10} These medications have varying developmentally-regulated mechanisms of action and potential adverse effects.^{16, 17} They have not been extensively studied in preterm neonates, and none are currently labeled by the United States (US) Food and Drug Administration for use in this population. Several randomized controlled trials (RCTs) have compared vasoactive medications in neonates with hypotension and have not demonstrated clear superiority of any one drug.^{18, 19, 20, 21, 22} In the absence of data to guide use of antihypotensive therapies such as vasoactive medications, it is not surprising that there is significant practice variation between centers in both intervention thresholds and treatment of early hypotension in preterm neonates.^{10, 11, 23, 24, 25} Evidence suggests that while the incidence of hypotension in ELGANs has remained relatively stable, treatment strategies have changed, including an overall decline in the use of vasoactive medications.^{8, 23, 24, 25} Whether this observation is related to a higher BP threshold for intervention, increased comfort with cautious observation in some neonates, or some other practice variation is unknown. The objective of this study is to provide updated data on the use of vasoactive medications during the first postnatal week among ELGANs cared for at US neonatal intensive care units (NICUs) from 2009-2018.

METHODS

Study design

We identified neonates born at 22-27 weeks gestational age (GA) and cared for at US Pediatrix Medical Group NICUs from 2009-2018. We excluded neonates if they had a major congenital anomaly, congenital heart disease (excluding isolated patent ductus arteriosus, atrial septal defect, or patent foramen ovale), were outborn, or received no medications (as these neonates were likely to have either missing data or have received comfort care only). Neonatal demographic and clinical data were obtained from the Pediatrix BabySteps Clinical Data Warehouse (CDW).²⁶ The CDW contains de-identified data extracted from clinical care documentation including patient demographics, medical history, diagnoses, medications, and laboratory results. This study was approved by the Duke University Health System Institutional Review Board with a waiver of informed consent.

Definitions

We included data on receipt of vasoactive medications (dopamine, dobutamine, epinephrine, norepinephrine, vasopressin, and milrinone) during the first postnatal week for any clinical indication and any duration of use. We defined bacteremia as any blood culture positive with an organism not typically considered a contaminant prior to postnatal day 7. For blood cultures positive for coagulase-negative *Staphylococcus* (CoNS), we defined definite CoNS bacteremia as 2 positive cultures on the same day²⁷ and probable CoNS bacteremia as 2 positive cultures for CoNS within a 4-day period, 3 positive cultures within a 7-day period, or 4 positive cultures within a 10-day period.²⁸ We included definite and probable CoNS bacteremia in the analysis.

Statistical methods

We used descriptive statistics such as frequencies (with percentages) and medians (with 25th and 75th percentiles) to describe discrete variables and continuous variables, respectively. We compared the distribution of demographic and clinical characteristics between neonates with and without any vasoactive medication exposure during the first postnatal week using the Chi-squared test. We used the Kruskal-Wallis or Chi-squared test to compare the distribution of vasoactive medication use, the concurrent use of 2 or 3 vasoactive medications, the distribution of the postnatal start day of treatment, and the total duration of treatment with vasoactive medication(s) by GA group. We used the Chi-squared test to compare the proportions of neonates exposed to the total number of vasoactive medications, each individual vasoactive medication, and combinations of vasoactive medications during the first postnatal week between 2 epochs (2009-2013 and 2014-2018). These 5-year epochs were chosen to compare exposure to vasoactive medications among similar numbers of ELGANs. P-values <0.05 were considered statistically significant. All analyses were conducted using Stata version 16.0 (College Station, TX).

RESULTS

Between 2009-2018, a total of 34 234 ELGANs cared for at 345 Pediatrix NICUs met inclusion criteria. This cohort of neonates had a median GA of 26 weeks (25th, 75th

percentiles: 24, 27) and median birth weight of 779 g (635, 930). A total of 10 070 (29%) neonates were exposed to 1 vasoactive medication in the first postnatal week (Table 1). Among neonates who received a vasoactive medication, 8331/10 070 (83%) initiated therapy on postnatal day 0 or 1 and the median number of days of exposure was 3 (25th, 75th percentiles: 1, 4) (Table 2). Earlier GA was associated with exposure to a greater number of vasoactive medications for a greater number of days. There were significant differences in all demographics for ELGANs with and without exposure to vasoactive medications (Table 1). Exposure was more common with lower GA; 328/548 (60%) of neonates born at 22 weeks were exposed compared with 1388/9493 (15%) at 27 weeks. Exposure was highest among ELGANs in the lowest birth weight category of <500 g. ELGANs with vasoactive medication exposure were more likely to be male, SGA, non-white race, and born by cesarean section; they were significantly less likely to have received antenatal corticosteroids. They were also more likely to have a 5 minute APGAR score <5, require mechanical ventilation, receive surfactant and/or systemic corticosteroids, and have bacteremia.

The most frequently used vasoactive medication was dopamine, followed by epinephrine, dobutamine, milrinone, vasopressin, and norepinephrine (Table 2). Use of milrinone, vasopressin, and norepinephrine was uncommon (<1% of ELGANs for each). A total of 2649/34 234 (7.7%) ELGANs received 2 vasoactive medications and 571/34 234 (1.7%) received 3 vasoactive medications. The most common medication combinations were dopamine plus dobutamine and dopamine plus epinephrine (Table 2). From 2009-2013 to 2014-2018, there was a statistically significant decrease in the percentage of ELGANs exposed to vasoactive medications (31% vs 28%, $p<0.001$). There was a statistically significant decrease in the use of dopamine and dobutamine, whereas use of vasopressin increased (Table 3, Figure 1). There was no significant change in the use of epinephrine, norepinephrine, or milrinone. Initial exposure to vasoactive medications occurred later and was for shorter duration in 2014-2018 compared with 2009-2013 (Table 3).

DISCUSSION

The diagnosis of early hypotension in preterm neonates is controversial. Early neonatal BP is influenced by a number of factors, including GA, postnatal age, and birth weight.^{2, 4, 10, 11, 24, 29, 30, 31, 32, 33, 34} In ELGANs, these relationships are less clear and early BP measurements can vary widely.^{2, 31} Receipt of antenatal corticosteroids and delayed cord clamping are associated with higher early BP, whereas conditions such as perinatal asphyxia and sepsis can result in low BP.^{2, 24, 29, 31, 35} In ELGANs, additional factors that cause or exacerbate hypotension include immature myocardium, relative adrenal insufficiency, patent ductus arteriosus, and decreased venous return related to the use of positive pressure ventilation.^{36, 37, 38}

This study evaluated the use of vasoactive medications during the first postnatal week among ELGANs cared for at Pediatrix NICUs from 2009-2018. Similar to prior database studies,^{8, 24, 25} we found that a substantial proportion (29%) of ELGANs were exposed to 1 vasoactive medication. The majority (83%) of these neonates began treatment within 2 days of birth. Treatment was associated with lower GA, lower birth weight, male sex, SGA status,

non-white race, and a lack of antenatal corticosteroids. Not unexpectedly, markers of illness severity such as 5 minute APGAR score <5, bacteremia, receipt of surfactant, and need for mechanical ventilation, were also associated with treatment.

Prior observational studies and practice surveys have identified dopamine as a first-line agent for hypotension in neonates.^{23, 24, 25, 39} We found that in our cohort of ELGANs, dopamine remained the most frequently prescribed vasoactive medication, followed by epinephrine and dobutamine. This finding aligns with another US database study showing that use of epinephrine surpassed that of dobutamine in the mid-2000s as a result of an overall decline in the use of dobutamine.²³ Use of norepinephrine, vasopressin, and milrinone was infrequent in our study cohort (<1% of neonates each), though there was a small increase in the proportion of neonates exposed to vasopressin in 2014-2018 compared with 2009-2013. Unfortunately, we did not have data on the indication for use of specific vasoactive medications. For example, milrinone is typically used in full term neonates to lower pulmonary vascular resistance in the setting of pulmonary hypertension. This issue is less common in ELGANs, which may explain the low rates of milrinone use in our study cohort. Also, at some centers, dopamine is often used in preterm neonates to increase renal perfusion for oliguria (in the presence or absence of hypotension). As we did not have access to BP values or urine output, some of these ELGANs may have received dopamine for the primary indication of oliguria rather than hypotension. Finally, we may have included use of epinephrine boluses for cardiac arrest or bradyarrhythmias in either the delivery room or NICU, in accordance with Neonatal Resuscitation Program guidelines. Despite the potential inclusion of ELGANs exposed to vasoactive medications for indications other than hypotension, the distribution of exposure to individual vasoactive medications did not differ significantly from those reported in other US database studies.^{23, 25}

Prior studies have shown declining rates in the treatment of early neonatal hypotension.²³ Between 2009-2018, the overall proportion of ELGANs exposed to vasoactive medications at Pediatrix NICUs also decreased slightly from 31 to 28% ($p<0.001$). This was driven by the decreased use of dopamine and dobutamine, a trend also observed from 2001-2012 among US Pediatric Health Information System (PHIS) database centers.²³ Vasoactive medications were started later, and used for a shorter duration in 2014-2018 compared with 2009-2013. As we did not have access to vital signs (including BP), we cannot relate this finding to the incidence of hypotension or the threshold(s) used for intervention. It is also possible that another practice change, such as increased use of antenatal or postnatal corticosteroids, contributed to the decreased use of vasoactive medications.

This study contributes to the limited evidence on the use of vasoactive medications in ELGANs, and has several strengths. First, it provides updated data on the use of vasoactive medications over a recent 10-year period. Second, the study cohort encompasses a generalizable population of ELGANs cared for by a large number of US NICUs. The Pediatrix Medical Group includes NICUs in 35 states, as well as Puerto Rico, which care for nearly 25% of the US's NICU patients. Third, we focused specifically on extremely preterm neonates, a group for which data on medication safety and efficacy is lacking. By demonstrating the frequent "off-label" use of vasoactive medications in ELGANs, this study provides justification for prospective safety and efficacy research.

There are limitations to this study. First, we did not have access to vital signs, including BP. As a result, we could not evaluate differences in BP treatment thresholds between individual neonates or between centers. We also could not evaluate the severity or duration of hypotension, how quickly BP increased, or if BP was “overcorrected.” Second, we did not have data on the indications for use of vasoactive medications, which may have been for reasons other than systemic hypotension (for example, use of epinephrine for delivery room resuscitation). Third, we did not have data on receipt of intravenous fluid boluses, total fluids per day, or medication doses, so we could not evaluate the impact of these factors on the use of vasoactive medications. Finally, we did not evaluate the association between vasoactive medication exposure and clinical outcomes such as death. There are inherent challenges to studying the relationship between treatment for hypotension, hypotension itself, and negative outcomes, as it is difficult to control for illness severity. In this retrospective study, we did not have data on BP or other important clinical indicators of illness severity such as receipt of cardiopulmonary resuscitation or blood gas values. This challenge highlights the need for prospective research on the management of hypotension and clinical outcomes in this population.

In conclusion, ELGANs are at high risk for hypotension and treatment with vasoactive medications during the first postnatal week. There is controversy regarding the definition and management of hypotension in this population, with limited evidence to support best practices. We found that a substantial proportion of ELGANs cared for at Pediatric NICUs from 2009-2018 were exposed to vasoactive medications, though overall use of vasoactive medications decreased slightly over the study period. Whether this observation reflects a higher threshold for treatment or another practice change, such as increased use of antenatal or postnatal corticosteroids, delayed cord clamping, or avoidance of mechanical ventilation, is not clear. Early hypotension in ELGANs is a complex and often multifactorial problem that requires an individualized approach. Newer technologies such as near-infrared spectroscopy and functional echocardiography may augment traditional hemodynamic monitoring and help tailor treatment.^{40, 41} Data from clinical trials is needed to better delineate which ELGANs benefit from treatment of hypotension and which can be cautiously observed, though issues relating to eligibility and enrollment can pose major challenges for investigators.⁴² Finally, given the frequent “off-label” use of vasoactive medications in preterm neonates, particularly in the first 1-2 postnatal days, prospective efficacy and safety studies are greatly needed.

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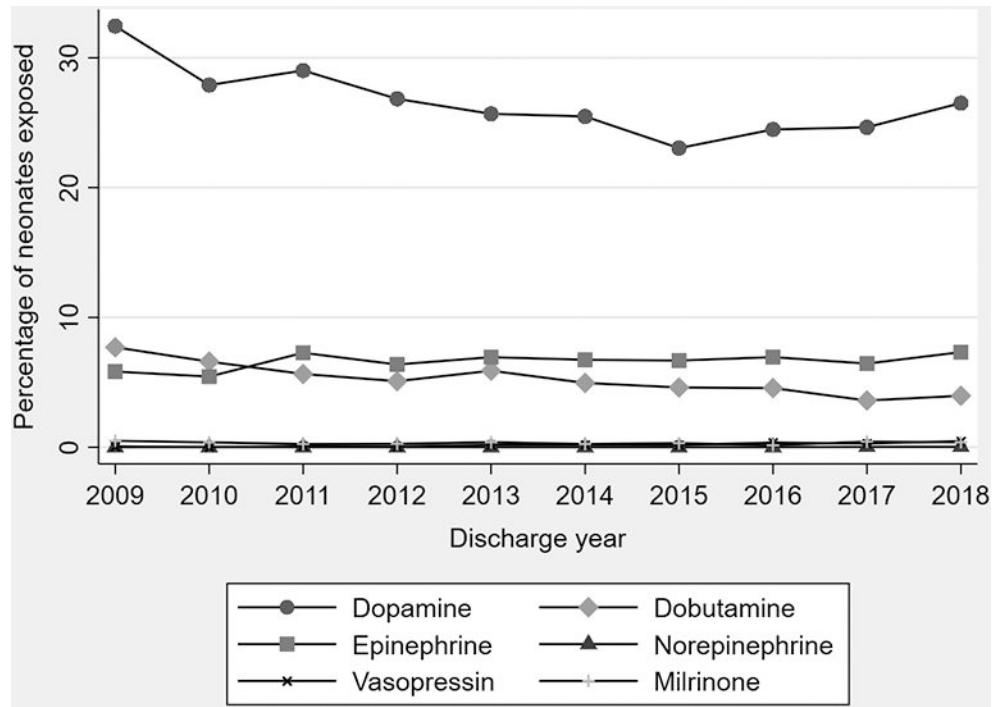


Figure 1. Vasoactive medications in ELGANs during the first postnatal week, 2009-2018.

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Table 1:

Demographics and clinical characteristics by vasoactive medication exposure during the first postnatal week, 2009-2018

	Vasoactive med. exposure		<i>p</i> -value †
	Yes N=10 070	No N=24 164	
Gestational age (weeks), N (%)			<0.001
22	328 (3)	220 (0.9)	
23	1868 (19)	1612 (7)	
24	2549 (25)	3457 (14)	
25	2201 (22)	4649 (19)	
26	1736 (17)	6121 (25)	
27	1388 (14)	8105 (34)	
Birth weight (g), N (%)			<0.001
<500	1176 (12)	902 (4)	
500-749	5243 (52)	7933 (33)	
750	3651 (36)	15 329 (63)	
Male, N (%)	5650 (56)	12 403 (51)	<0.001
SGA, N (%)	2057 (21)	2907 (12)	<0.001
White race, N (%)	3734 (39)	9441 (41)	<0.001
Cesarean section, N (%)	7329 (74)	16 721 (70)	<0.001
5 min. APGAR score <5, N (%)	3502 (36)	4607 (19)	<0.001
Antenatal steroids, N (%)	7922 (79)	20 406 (84)	<0.001
Mechanical ventilation, N (%) *	9765 (97)	19 125 (79)	<0.001
Surfactant, N (%)	9168 (91)	19 535 (81)	<0.001
Systemic corticosteroid, N (%) *	2585 (26)	601 (2)	<0.001
Bacteremia, N (%) *	528 (5)	637 (3)	<0.001

* Prior to postnatal day 7

† *p*-value for Chi-squared test

Table 2: Trends in vasoactive medication use during the first postnatal week by gestational age, 2009-2018

	Gestational age at birth (weeks)							Total N=34 234	p-value [†]
	22 N=548	23 N=3480	24 N=6006	25 N=6850	26 N=7857	27 N=9493			
Vasoactive med. exposure, N (%)	328 (60)	1868 (54)	2549 (42)	2201 (32)	1736 (22)	1388 (15)	10 070 (29)	<0.001	
Number of vasoactive meds., N (%)								<0.001	
1	196 (36)	1225 (35)	1874 (31)	1651 (24)	1370 (17)	1105 (12)	7421 (22)		
2	110 (20)	500 (14)	523 (9)	431 (6)	290 (4)	224 (2)	2078 (6)		
3	22 (4)	136 (4)	145 (2)	111 (2)	72 (0.9)	52 (0.6)	538 (2)		
4	0 (0)	7 (0.2)	7 (0.12)	8 (0.1)	4 (0.1)	7 (0.1)	33 (0.1)		
Dopamine, N (%)	283 (52)	1675 (48)	2301 (38)	2004 (29)	1574 (20)	1258 (13)	9095 (27)	<0.001	
Epinephrine, N (%)	116 (21)	541 (16)	591 (10)	458 (7)	307 (4)	246 (3)	2259 (7)	<0.001	
Dobutamine, N (%)	79 (14)	410 (12)	449 (7)	381 (6)	273 (3)	200 (2)	1792 (5)	<0.001	
Milrinone, N (%)	1 (0.2)	17 (0.5)	27 (0.5)	26 (0.4)	20 (0.3)	21 (0.2)	112 (0.3)	0.05	
Vasopressin, N (%)	3 (0.6)	18 (0.5)	14 (0.2)	9 (0.1)	7 (0.1)	13 (0.1)	64 (0.2)	<0.001	
Norepinephrine, N (%)	0 (0)	0 (0)	1 (<0.1)	0 (0)	1 (<0.1)	0 (0)	2 (<0.1)	0.70	
2 med. combinations, N (%)									
Dopa. + Dobuta.	72 (13)	365 (10)	395 (7)	328 (5)	227 (3)	161 (2)	1548 (5)	<0.001	
Dopa. + Epi.	75 (14)	387 (11)	392 (7)	307 (4)	185 (2)	152 (2)	1498 (4)	<0.001	
Dopa. + Norepi.	0 (0)	0 (0)	1 (<0.1)	0 (0)	1 (<0.1)	0 (0)	2 (<0.1)	0.70	
Dopa. + Vaso.	1 (0.2)	14 (0.4)	11 (0.2)	8 (0.1)	6 (0.1)	11 (0.1)	51 (0.2)	0.002	
Dopa. + Milrinone	1 (0.2)	15 (0.4)	24 (0.4)	20 (0.3)	17 (0.2)	19 (0.2)	96 (0.3)	0.09	
Other	4 (1)	11 (0.3)	11 (0.2)	13 (0.2)	10 (0.1)	7 (0.1)	56 (0.2)	0.001	
3 med. combinations, N (%)									
Dopa. + Epi. + Vaso.	0 (0)	6 (0.2)	8 (0.1)	5 (0.1)	1 (<0.1)	6 (0.1)	26 (0.1)	0.04	
Dobuta. + Epi. + Vaso.	1 (0.2)	4 (0.1)	3 (0.1)	3 (<0.1)	0 (0)	3 (<0.1)	14 (<0.1)	0.05	
Other	21 (4)	136 (4)	144 (2)	113 (2)	75 (1)	53 (0.6)	542 (2)	<0.001	
Postnatal start day of first vasoactive med., N (%)								<0.01	
0	213 (65)	1099 (59)	1441 (57)	1263 (57)	970 (56)	777 (56)	5763 (57)		
1	87 (27)	471 (25)	653 (26)	522 (24)	472 (27)	363 (26)	2568 (26)		

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	Gestational age at birth (weeks)						Total N=34 234	p-value [‡]
	22 N=548	23 N=3480	24 N=6006	25 N=6850	26 N=7857	27 N=9493		
2	14 (4)	91 (5)	139 (5)	158 (7)	115 (7)	112 (8)	629 (6)	
3	2 (0.6)	53 (3)	109 (4)	83 (4)	55 (3)	59 (4)	361 (4)	
4	3 (0.9)	42 (2)	71 (3)	61 (3)	39 (2)	32 (2)	248 (2)	
5	5 (2)	55 (3)	69 (3)	51 (2)	52 (3)	29 (2)	261 (3)	
6	4 (1)	57 (3)	67 (3)	63 (3)	33 (2)	16 (1)	240 (2)	
Days of exposure, median (25 th , 75 th %)	2 (1,4)	2 (1,5)	3 (1,5)	3 (1,5)	3 (1,4)	3 (1,4)	3 (1,4)	<0.001

[‡] p-value for Kruskal-Wallis or Chi-squared test

Trends in vasoactive medication use during the first postnatal week by time period, 2009-2018

Table 3:

	2009-2013 N=16 908	2014-2018 N=17 326	<i>p</i> -value [‡]
Vasoactive med. exposure, N (%)	5236 (31)	4834 (28)	<0.001
Total number of vasoactive meds., N (%)			<0.001
1	3815 (23)	3606 (21)	
2	1106 (7)	972 (6)	
3	305 (2)	233 (1)	
4	10 (0.1)	23 (0.1)	
Dopamine, N (%)	4791 (28)	4304 (25)	<0.001
Epinephrine, N (%)	1076 (6)	1183 (7)	0.08
Dobutamine, N (%)	1043 (6)	749 (4)	<0.001
Milrinone, N (%)	59 (0.4)	53 (0.3)	0.49
Vasopressin, N (%)	13 (0.1)	51 (0.3)	<0.001
Norepinephrine, N (%)	0 (0)	2 (<0.1)	0.16
Postnatal start day of vasoactive med., N (%)			<0.001
0	3109 (59)	2654 (55)	
1	1356 (26)	1212 (25)	
2	288 (6)	341 (7)	
3	170 (3)	191 (4)	
4	113 (2)	135 (3)	
5	111 (2)	150 (3)	
6	89 (2)	151 (3)	
Days of exposure, median (25 th , 75 th %)	3 (2,5)	2 (1,4)	<0.001

[‡] *p*-value for Chi-squared test or Wilcoxon rank sum test