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Epidemiology of Necrotizing Enterocolitis Temporal Clustering in Two Neonatology Practices

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Abstract

Objective—To develop a statistical method for defining clusters of necrotizing enterocolitis (NEC) cases in the neonatal intensive care unit (NICU).

Study design—2782 infants, between 1996–2004, weighing 401–1500 grams at birth were included. NEC was defined as Bell stage II or III. Two statistical methods used to define “disease clusters” were: (1) modified scan test; (2) comparison of observed and expected incidence density rates (IDR) of NEC at each NICU.

Results—The proportion of infants with NEC was similar between NICUs (7.1% vs. 7.7%; $p=0.6$) as was the expected IDR of NEC (1.39/1000 patient-days vs. 1.32/1000 patient-days, $p=0.72$). Twelve temporal clusters of NEC were identified in the NICUs combined, comprising 18% of 203 total NEC cases during the study period. No seasonal/secular trends were noted for NEC rates or identified clusters. Potential NEC clusters of ≥ 3 cases at either NICU had >75% chance of being a true NEC cluster.

Conclusions—No operational definition of NEC cluster exists. This study introduced methods to be employed for prospective surveillance and guide studies to investigate etiologic relevance. Utilizing the proposed methods, statistically significant clusters (potential outbreaks) of NEC within NICUs can be identified early, providing early opportunity to implement cluster investigation protocols.

Keywords

disease clusters; outbreaks; neonatal intensive care unit; very low birth weight infants

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Necrotizing enterocolitis (NEC), the most common gastrointestinal emergency in the neonatal intensive care unit (NICU), is a sudden-onset life-threatening disease that occurs primarily in preterm infants. NEC affects approximately 6–10% of very low birthweight (VLBW) infants, ^{1–4} with nearly 90% of all NEC cases occurring among this population and a case-fatality rate as high as 20–40%.⁵ The etiology of NEC is not clearly established, but appears to be multifactorial, involving enteral feeding, vascular or perfusion-related gastrointestinal compromise, and bacterial invasion.^{6, 7} Cases appear to occur sporadically with reports of clusters or outbreaks.^{8, 9} No formal or consistent approach has been applied to these reports, however, regarding the definition and timing of apparent outbreaks or the cases associated with them. The case definition applied during outbreak investigations has often included suspected NEC and gastroenteritis cases, with outbreak durations of 8 to 10 weeks.^{10–21}

An important clue to understanding the etiology of NEC is to understand the extent to which cases aggregate in a specific space and time as clusters, occur sporadically, or form clusters by chance alone. Fundamentally, there is no standard definition of a NEC cluster that might allow an investigator to determine whether a specific instance of several cases closely related in time represents a significant grouping. As a result, clusters or outbreaks of NEC tend to be defined subjectively; the detection and ascertainment of a cluster lie with observations.

A few large scale outbreaks occurring simultaneously at different sites have provided evidence of the potential for geographic and temporal clustering of NEC.^{12, 14, 22–24} The occurrence of temporal clusters provides potential support for an infectious or common exposure etiology of NEC.^{25, 26} In order to determine whether temporal clustering of NEC occurs within a site that experiences endemic NEC, we proposed a systematic study using registry data collected as part of the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network. The objective of this study was to develop a statistically reliable method for defining clusters or outbreaks of NEC cases and to describe the pattern of NEC clusters. Because we are not addressing a specific cause or pathogen in relation to NEC to avoid confusion associated with the use of different nomenclature (disease outbreaks versus disease clusters), we have addressed the occurrence of NEC clusters for this statistical study.

Methods

Data for this retrospective cluster analysis were abstracted from the NICHD Neonatal Research Network registry of very low birthweight infants who weighed between 401 and 1500 grams at birth and were born at or admitted to either of two Cincinnati Level III NICUs between 1996 and 2004. A third Level III NICU was not included in this study because it is part of a children's hospital and does not contain a birthing center. Only 10 cases of NEC occurred at the excluded NICU over the course of the study period. As part of the Network's registry, all very low birth infants who were born in the Cincinnati region and developed NEC are captured in the registry. The Cincinnati region has approximately 30,000 annual births. A NEC case was defined using the modified Bell's staging criteria of stage IIA, IIB or IIIA (proven with no surgery including distension and/or signs of peritonitis, with x-ray evidence of pneumatosis intestinalis) or stage IIIB (NEC confirmed at surgery).²⁵ The staging of NEC was recorded by clinicians using clinical and radiological information. Charts were reviewed and diagnosis was verified and recorded into the registry by trained research nurses. Infants who died within the first 24 hours of life were excluded from the analysis, as these infants would not have had the opportunity to either develop NEC or to be exposed to potential factors that may make them susceptible to NEC. Infants who survived beyond 24 hours were included because they would have had the opportunity to develop NEC. NEC onset was defined as the date in which the first clinical or radiological sign was recorded.

Statistical analyses

The incidence of NEC was defined as the number of newly developed cases of NEC per 100 admissions. The incidence density rate (IDR) was defined as the number of newly developed NEC cases per 1000 patient-days. The IDR of NEC for the specified window of 7 days was compared with an overall average IDR calculated for years 1996–2004 (i.e., the baseline rate for each NICU). Poisson regression was used to determine seasonal and secular trends in NEC rates.

Clusters were identified and defined based on two statistical methods. First, to identify potential clusters, we applied a modified version of the scan test reported by Grimson and Mendelsohn.²⁷ This test employs the binomial distribution to detect current clusters of one or more days duration during the ongoing data collection and monitoring process. For the purpose of this study, we used this test retrospectively, in the same manner as reported by Grimson and Mendelsohn.²⁷ Because possible mechanisms of NEC transmission are unknown, uncertainty exists with regard to defining an important cluster window. A seven day window duration was based on subjective input from clinicians focusing on time frames during which cases may be considered as clustered. For each year, a time period of 7 days was selected to scan the time frame of 30 days. The maximum number of cases was counted in each time window and probability of less than 0.05 was used to identify statistically significant clusters.

Once statistically significant clusters were identified, a second test was applied which used the IDR of NEC calculated during the current cluster period compared with the baseline IDR of NEC for each NICU. The observed IDR of NEC was calculated for the same 7-day window that was identified as statistically significant during the scan test. This type of comparison investigated the possibility that potential clustering of cases may coincide with an increase in the overall rate of disease. The Fisher Exact p-value, with a level of significance < 0.01 , was used to determine statistical significance when comparing observed and expected IDRs.

The combined occurrence of statistical significance by both methods above defined a consistent cluster. The label of inconsistent cluster was applied when a group of NEC cases was found to be statistically significant by the scan test but not by comparing the observed with expected IDRs. Sporadic cases were isolated events (no other cases within a 7-day window) or cases that appeared temporally close to one another (within 7 days of each other), but were not statistically significant based on the scan test. The methods described above were applied to each NICU to test for temporal clustering of NEC.

Using the two different methods of cluster detection helped to control for the possibility that an increase in NEC cases were associated with an increase in the number of extremely low birth weight infants (ELBW) who are at high risk for developing NEC. The scanning method allowed us to take into account how many previous NEC cases occurred in the past 30 days. Thus high numbers of NEC cases, possibly due to high numbers of ELBW infants in the past 30 days, would influence the significance of potential clusters of NEC in the most recent 7 days by making current clusters harder to detect statistically. We then used an incidence density measure of NEC to determine if the current rate seen was significantly higher than the rate of NEC that was expected within that particular NICU. This calculation takes into account the number of NICU-days of all infants at risk. In addition, no pattern was seen regarding the proportion or number of ELBW infants admitted to the NICU in the month prior to a cluster onset.

Results

Between 1996 and 2004, 2857 infants were admitted to the two NICUs. Seventy-five infants died within the first 24 hours. No case of NEC occurred in the first 24 hours of life. An additional

98 infants died within the first week of life. Two of these infants developed NEC, one on day of life 5 and one on day of life 6. Among the 2782 included infants, there were 203 cases of NEC. The mean (standard deviation) gestational age of the study population was 28.2 (2.7) weeks. The mean (SD) gestational age of infants who developed NEC was 26.8 (2.2) weeks and the mean (SD) age of the onset of NEC was 18.2 (13.5) days. The proportion of infants with NEC did not significantly differ between NICU A and NICU B (7.1% vs. 7.7%, $p=0.6$). Between 1996 and 2004, NICU A reported 122 cases of NEC in 88,070 patient-days, for an incidence density rate (IDR) of 1.39 per 1000 patient-days [95% CI 1.14, 1.64]. NICU B reported 81 cases of NEC in 61,630 patient-days, for an IDR of 1.32 cases per 1000 patient-days [95% CI 1.03, 1.61] (Table I and Figure 1). There was no significant difference in rates between the two sites ($p=0.72$). The incidence of NEC did not consistently increase over time for either NICU ($p=0.4$ for both NICUs) through Poisson regression. Seasonal occurrence of NEC was examined through Poisson regression (Figure 2; available at www.jpeds.com). The overall rates of NEC were similar across seasons at both NICUs ($p>0.5$ for both NICUs, Figure 2).

Temporal Clustering of Necrotizing Enterocolitis by NICU

Using the modified scan test alone for detecting potential clustering of NEC at NICUs A and B, a total of 41 potential site-specific clusters were identified for the years 1996 through 2004; 28 occurred at NICU A and 13 occurred at NICU B (Table II; available at www.jpeds.com). Among the 203 cases included in this analysis, 52% ($n=106$) were sporadic cases. Of the 41 potential clusters, 27 (66%) were comprised of only two NEC cases. There were no differences in the proportion of potential clusters that were comprised of two cases between sites A and B (68% vs. 62% respectively, $p=0.7$). Twelve potential clusters (29%) were defined as consistent clusters (classified by both methods); seven consistent clusters from NICU A and five consistent clusters from NICU B.

Of the total 203 NEC cases that occurred at these sites, 18% ($n=37$) occurred as part of a defined consistent cluster. The proportion of total NEC cases that occurred in a cluster did not differ between sites (18% vs. 18.5% respectively, $p=0.8$). Of the 29 inconsistent clusters, 27 were comprised of only two cases of NEC (i.e., all two-case clusters identified by the scan test). Most of the potential clusters that were comprised of three cases of NEC (85%, $n=11$) were considered as consistent clusters by both methods. Year 2001 had the highest proportion of NEC cases that were defined as clusters for both NICUs; 67% ($n=10$) of 15 cases in NICU A and 50% ($n=6$) of 12 cases in NICU B were defined as consistent clusters (Figure 3). Four of the 12 clusters occurred in the spring months (3 at NICU A), and four occurred in the autumn months (two at each site).

Table III summarizes the percent of clusters that were identified as “true” or consistent clusters using both statistical methods for each site. In a NICU that has a baseline rate of NEC that is approximately 7%, the probability that the occurrence of three NEC cases in a 7-day window is a true cluster is 75%.

Discussion

A few large scale outbreaks occurring simultaneously at different sites have provided evidence of the potential for geographic and temporal clustering of NEC.^{12, 14, 22–24} The occurrence of temporal clusters provides potential support for a common exposure etiology of NEC.^{25, 26} There is at present no generally accepted operational definition of a NEC cluster. According to this study’s definition of a consistent cluster, 11 temporal clusters occurred within two NICUs; seven at NICU A and four at NICU B. Among the 203 cases of NEC that occurred at the two sites during the study period, 18% occurred within a defined cluster, and 52% of cases occurred sporadically. From the perspective of identifying a common pathogenesis, the

importance of this finding lies with the usefulness of a simple algorithm for detecting or identifying the occurrence of a cluster. For example, according to the findings of the current study, two NEC cases close together in time would not be considered a cluster. However, three or more NEC cases within the specified window have a high probability (>75%) of being a true cluster as classified by the concordance of two methods. Given these findings, clinical epidemiologists may decide that once three cases occur within seven days there is statistical justification for exploring a common pathogenesis.

Though most NEC cases occur sporadically, NEC “epidemics” have been reported in the literature, with the number of cases, clinical presentations, and potential causative agents (e.g. pathogen-specific NEC) differing greatly. In 1972, Stein et al reported one of the first outbreaks consisting of 11 cases of NEC in a single nursery in South Africa over a 10-week period.¹⁰ Chappell and Dinner reported an outbreak involving 20 cases over a 3-week period.²⁹ Rotbart and Levin described a 7-year period in which 193 cases of NEC occurred, with intermittent outbreaks that led to a closure of the nursery.⁹ Book et al described 67 cases in a 4-year period, of which 42 cases occurred in a 10 month period.²² In 1979, Guinan et al reported three “epidemics” in three different high-risk nurseries, all occurring within the same period.¹² Chaney et al reported on temporal clustering of NEC occurring in two different maternity hospitals in Paris in 1982,¹⁴ and Faustini et al, in 2004, reported temporal clustering of NEC within two different neonatal units simultaneously.²³ Our study utilized analytic techniques to identify the temporal clustering of NEC; previous studies relied on intuitive or ad-hoc definitions only.

Many studies on outbreaks of NEC reported either very low rates of NEC^{11–13, 17, 19, 22, 31} or did not report a background rate,^{10, 14, 15, 18, 29, 32} leading the reader to assume that perhaps that particular site typically sees a minimal number of NEC cases within their institution. Our NICUs have a relatively endemic rate of NEC. Because most studies that report NEC outbreaks appear to originate from sites that do not typically report a baseline incidence of NEC, there is likely to be a reporting bias. Institutions that care for preterm infants, and have an incidence rate of NEC comparable to the literature (i.e. ~7% among VLBW infants), may not be reporting periods during which an increase in the number of NEC events occurs close in time. It is probable that institutions which consider NEC to be endemic are not at heightened awareness of this type of clustering. Some investigators also described both NEC (suspected and proven) and gastroenteritis cases occurring simultaneously.^{10, 16, 23, 32, 33} Our study focused on a standardized definition of NEC in order to minimize the over-identification of clusters by including non-proven (suspect) NEC cases. This NEC definition required the presence of pneumatosis intestinalis, which likely excludes cases of spontaneous intestinal perforations.³⁴

NEC in infants with selected congenital anomalies may occur as a result of a different pathogenesis compared with premature infants without congenital anomalies. We included this small subset of infants for several reasons. It was not a purpose of this study to address factors that may increase the risk of NEC among VLBW infants, but to provide methods for detecting potential clusters of NEC statistically. Without understanding fully the pathogenesis of NEC for each infant, we did not want to risk missing any infant that could feasibly contribute to a cluster of NEC. Only three NEC cases, all of whom were premature, had a congenital anomaly: duodenal atresia (1), tetralogy of Fallot (2).

Numerous methods for evaluating clusters have been summarized.^{35, 36} Although previous scan tests have been proposed for temporal clustering,^{37–44} the methods for the current study were chosen for several reasons. The test proposed by Grimson and Mendelsohn is based on a binomial distribution that allows for the detection of current clusters of one or more days duration during ongoing monitoring.²⁷ The methods used in the current study are easily applied

by clinicians, allowing for alteration of the scan window. These proposed methods require only assumptions based on the NICU of interest (e.g., baseline NEC rates). Baseline rates of NEC can easily be calculated for individual sites and previous known cases can be recorded with little difficulty.

The scan test assumes that the denominator remains static. Because the population within the NICUs on any given day may vary greatly, a second method of cluster identification was applied that accounted for variability in the actual number of patient-days-at-risk contributing to the denominator. It is important to note that all clusters identified by the scan test method alone containing only two events were later defined as inconsistent clusters when comparing the observed incidence rates with the background rate (Table III). This finding may speak to the importance of using two statistical methods for identifying a cluster. Because the scan test is based on the binomial distribution, results for the most recent time window (in this case 7 days) are dependent upon the number of NEC events in the previous 30 day window. If no other cases had occurred in the previous window of importance, an increase of only two NEC cases can become statistically relevant. A second level screen for potential temporal clustering of cases decreases the number of clusters identified based on a previous experience.

Because window length should be predetermined and meaningful to an “epidemic period” if such a period is definable,²⁷ and with no consensus as how this period should be defined for NEC, the cluster window of 7 days was used. This window was chosen as this duration seemed to be clinically meaningful within our institutions with regard to an important time frame for which the appearance of an excess of NEC cases might bring about a heightened awareness. Intervals of other lengths, however, may be selected for monitoring. A longer interval opens up the possibility of capturing more cases. However, by increasing the denominator (number of patient-days), the overall rate of NEC for the time period of interest may be decreased, and clusters that were significant with a 7-day window may no longer be statistically significant in a longer cluster window. Within institutions that would typically have background rates of NEC that are considerably lower than 7%, an interval wider than the 7-day window would be appropriate to identify possible outbreaks. Because it is possible to alter intervals of interest until statistically significant clusters are identified, it was important that a cluster window was defined *a priori*.

A number of problems are encountered in the study of clusters: the health events being investigated are usually rare, the increase in the number of events tends to be small and may occur over a long period, and information on the population at risk or on expected rates is often unavailable.³⁶ Although periods of time existed in which no cases occurred in the current study, the overall background rate for the disease was approximately 7%, with an incidence density rate of 1.3 per 1000 patient-days at both institutions. Therefore, we were able to compare the rate of NEC during a suspected cluster with an expected rate.

A major statistical issue regarding the use of cluster detection methods lies in the Type I and Type II error rates. We reduced the chance of a false positive (Type I error) by using an alpha level of 0.01 for the IDR comparisons, instead of the conventional 0.05. The process of a daily scan creates a large number of multiple comparisons, making preset rejection levels for p-values (e.g. Bonferroni adjustments) so small that the power to detect actual clusters may not be adequate. With the possibility of missing a “real” cluster, using methods for multiple comparison adjustments are not always recommended.^{27, 45–47} If the goal is the early detection of outbreaks, a highly sensitive strategy is required to raise awareness of the possibility that the number of cases seen within a short time frame has become “too high” and could further warrant action steps to take certain precautions in the NICU.

This study has introduced methods that can be employed for prospective surveillance and help guide the design of studies to investigate etiologic relevance. We have illustrated a combination of statistical tests (a scan test and the comparison of observed vs. expected rates), that can be easily applied for weekly monitoring of temporal clustering of necrotizing enterocolitis. Using the proposed methods, statistically significant clusters, or potential outbreaks, of necrotizing enterocolitis within NICUs can be identified early, providing an opportunity to implement a cluster investigation protocol as early as possible. Practice guidelines for such a protocol may include the cohorting of infants, cohorting nursing care for affected infants to with NEC infants only, and evaluating and monitoring hand hygiene techniques.

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Abbreviations

NEC	necrotizing enterocolitis
NICU	neonatal intensive care unit
VLBW	very low birth weight
NICHD	National Institute of Child Health and Human Development
IDR	incidence density rate
FDR	false discovery rate

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Figure 1.

Incidence rate of necrotizing enterocolitis over time by NICU site. Baseline incidence density rate at each NICU for entire study period indicated by solid line at 1.39 cases per 1000 patient-days for NICU A and by dotted line at 1.32 cases per 1000 patient-days for NICU B.

Figure 2.
Overall seasonal necrotizing enterocolitis rate for 1996–2004.

Figure 3.

Proportion of total cases within defined consistent temporal clusters. Proportions of cases each year within consistent (“true”) clusters illustrated as black bars. Proportions of cases within inconsistent clusters illustrated as white bars, and sporadic cases are illustrated by hash marked bars. For example, in 2001, 37% of all NEC cases occurred within a defined consistent cluster. Numbers at the top of each bar represent the number of cases of NEC each year.

Table 1

Comparison of characteristics of neonatal intensive care units

	NICU A	NICU B
# Very low birth weight infants	1726	1056
# Patient-Days	88,070	61,630
# NEC cases	122	81
Proportion (95% CI) of infants with NEC	7.1% [5.9, 8.3]	7.7% [6.1, 9.3]
NEC requiring surgery - N (%)	78 (64%)	46 (57%)
Case fatality rate	45 (37%)	27 (33%)
Incidence density rate (95% CI) per 1000 patient-days	1.39 [1.14, 1.16]	1.32 [1.03, 1.61]
Mean (SD) length of stay ^a	50.8 (30.9)	58.0 (34.8)
Median (range) # NEC cases per year ^a	14 (8–17)	10 (4–13)
Median (range) duration in days between cases ^b	18 (0–170)	28 (0–218)

^a p<0.001;^b p<0.05;

Table 2

Temporal Clusters Identified By NICU

Cluster*	Year	# Cases	Incidence density rate [†]	Cluster Definition	Season [‡]
1-A	1996	2	9.3 [1.1, 33.6]	Inconsistent	Su
2-A	1996	2	10.3 [1.2, 37.2]	Inconsistent	Su
3-A	1996	3	10.1 [1.2, 36.5]	Inconsistent	A
4-A	1996	2	11.8 [1.4, 42.8]	Inconsistent	A
5-A	1997	2	9.1 [1.1, 32.8]	Inconsistent	W
6-A	1997	2	17.0 [2.1, 61.2]	Inconsistent	Sp
7-A	1998	3	14.2 [2.9, 41.4]	Consistent	Sp
8-B	1998	3	15.6 [3.2, 45.7]	Consistent	A
9-A	1998	3	14.4 [3.0, 42.2]	Consistent	W
10-A	1999	2	13.6 [1.6, 49.2]	Inconsistent	W
11-B	1999	2	11.2 [1.4, 40.6]	Inconsistent	Sp
12-A	1999	2	9.1 [1.1, 33.0]	Inconsistent	Sp
13-A	1999	2	9.7 [1.2, 34.9]	Inconsistent	Su
14-B	1999	2	17.0 [2.1, 61.2]	Inconsistent	Su
15-A	1999	2	8.8 [1.1, 31.8]	Inconsistent	A
16-A	1999	2	12.2 [1.5, 44.1]	Inconsistent	A
17-A	1999	2	13.3 [1.6, 47.9]	Inconsistent	W
18-A	2000	2	9.6 [1.2, 34.6]	Inconsistent	Sp
19-A	2000	3	17.1 [3.5, 50.1]	Consistent	Sp
20 ^S -B	2000	3	23.6 [4.9, 69.0]	Consistent	Su
21-B	2000	2	9.2 [1.1, 33.1]	Inconsistent	Su
22-A	2000	2	10.2 [1.2, 36.9]	Inconsistent	A
23-A	2000	2	8.5 [1.0, 30.7]	Inconsistent	W
24-A	2001	2	10.1 [1.2, 36.5]	Inconsistent	Sp
25 ^S -A	2001	4	17.6 [4.8, 45.1]	Consistent	Sp
26 ^S -B	2001	3	15.2 [3.1, 44.5]	Consistent	Su
27-A	2001	3	13.6 [2.8, 39.9]	Consistent	A
28-B	2001	3	19.4 [4.0, 56.6]	Consistent	A
29-A	2001	3	17.2 [3.6, 50.4]	Consistent	W
30-A	2002	2	10.2 [1.2, 36.7]	Inconsistent	Sp

Cluster*	Year	# Cases	Incidence density rate [†]	Cluster Definition	Season [‡]
31-A	2002	2	7.2 [0.9, 26.0]	Inconsistent	Sp
32-B	2002	3	21.7 [4.5, 63.5]	Consistent	Sp
33-B	2003	2	9.5 [1.1, 34.2]	Inconsistent	W
34-B	2003	2	11.9 [1.4, 43.0]	Inconsistent	Su
35-A	2003	2	6.1 [0.7, 21.9]	Inconsistent	Su
36-B	2003	2	13.5 [1.6, 48.8]	Inconsistent	A
37-B	2004	2	12.1 [1.5, 43.5]	Inconsistent	W
38-A	2004	3	8.2 [1.7, 24.1]	Inconsistent	W
39-B	2004	2	11.2 [1.4, 40.6]	Inconsistent	W
40-A	2004	2	6.6 [0.8, 23.9]	Inconsistent	Sp
41-A	2004	3	13.3 [2.7, 38.8]	Consistent	A

* "A" denotes NICU A and "B" denotes NICU B.

[†] 95% CI reported in brackets.

[‡] Sp=March, April, May; Su=June, July, August; A=September, October, November; W=December, January, February.

[§] Overlapping cluster.

Table 3

Percent of clusters identified as true or consistent clusters using both statistical methods for identification.

Size of potential cluster	Temporal clustering at NICU A		Temporal clustering at NICU B	
	Number of potential clusters identified by one method	Percent classified as a "true" cluster using both methods	Number of potential clusters identified by one method	Percent classified as a "true" cluster using both methods
2 cases	19	0	8	0
3 cases	8	75%	5	100%
4 cases	1	100%	0	--