

# Recurrent Bacteremia after Endoscopic Injection of N-butyl-2-cyanoacrylate for Gastric Variceal Bleeding

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### **Revised abstract**

**Background**: Gastric variceal bleeding is associated with a high mortality rate, and sclerotherapy using N-butyl-2-cyanoacrylate is the treatment of choice. The risk of recurrent bacteremia after N-butyl-2cyanoacrylate injection has rarely been reported. We aimed to evaluate the frequency of this complication following injection of N-butyl-2cyanoacrylate in a real-world setting.

**Methods**: We analyzed retrospective data from a single-center cohort of patients with liver cirrhosis who underwent N-butyl-2-cyanoacrylate injection for the treatment of bleeding gastric varices from January 2010 to March 2021. Recurrent bacteremia was defined as repeated bacteremia caused by the same microorganism after the resolution of the first event occurring at least two weeks from the date of the final positive blood culture of the first event.

Results: A total of 232 patients receiving 338 sessions of N-butyl-2cyanoacrylate injection were enrolled. For the purpose of this study, we excluded patients (n=39) with a follow-up duration of less than 3 weeks. We included 193 patients with liver cirrhosis and gastric variceal bleeding who received 298 sessions of N-butyl-2-cyanoacrylate injection and were followed up for ≥21 days. All patients received antibiotics prophylaxis; third-generation cephalosporins were used. The average age of patients was 60.0  $\pm$  12.3 years and the mean Model for End-Stage Liver Disease (MELD) score was  $13.5 \pm 5.4$ . Of the patients following cyanoacrylate injection, 60 patients developed primary bacteremia at a median of 323 (interquartile range, 66–932) days from N-butyl-2-cyanoacrylate injection. Nine out of 60 patients developed recurrent bacteremia following sclerotherapy with N-butyl-2cyanoacrylate. The identified organisms were: Extended-Spectrum ß-Lactamase (ESBL)-producing *Escherichia coli* (3), ESBL-producing Klebsiella pneumoniae (2), non-ESBL-producing Klebsiella pneumoniae Pseudomonas aeruginosa (1), and Methicillin-resistant Staphylococcus aureus (1). The median number of episodes of recurrent bacteremia per patient was 2 (range, 2–5) during the median 972 (range, 78–1997) days of follow-up. Four of these nine recurrent bacteremia patients died.

**Conclusion**: Recurrent bacteremia occurred in 4.7% of cirrhotic patients following cyanoacrylate injection for the treatment of gastric variceal bleeding. Foreign-body-type infection of the polymerized N-butyl-2cyanoacrylate should be suspected in patients who had received previous endoscopic treatment with N-2-butyl-cyanoacrylate and fails to disclose another source of infection.

## Background

- Gastric variceal bleeding is a serious complication of liver cirrhosis
- Endoscopic injection with N-butyl-2-cyanoacrylate is used worldwide for the acute gastric variceal bleeding
- Oral-pharyngeal contamination, the accessory channel, and a contam supply are assumed to be the sources of infection associated with endosc sclerotherapy
- N-butyl-2-cyanoacrylate (NBC; Histoacryl):
  - Polymerizes from liquid glue to a plastic cast on contact with blood in
  - Forms polymers within seconds, thus rendering hematogenous spread
  - In vitro antibacterial properties  $\rightarrow$  cyanoacrylate injection might invasion and reduce the frequency of bacteremia?
- Patients with active and recent bleeding may be susceptible to bacter through a defective variceal wall
- The foreign body of a glue plug offers an ideal surface for bacterial colon becomes a reservoir for continuous bacterial dissemination
- 30% of patients who underwent GVO had transient bacteremia and most in self-limited
- Recurrent or apparent bacteremia is rarely reported

## **Methods**

### Study design and hospital setting

- Retrospective, single center chart review study
- Study period: January 2010 to March 2021
- Inclusion criteria
- Liver cirrhosis who underwent endoscopic N-butyl-2-cyanoacrylate (His injection for the treatment of bleeding gastric varices
- N=232 **Exclusion criteria**
- Patients (n=39) with a follow-up duration of less than 3 weeks from Ncyanoacrylate injection
- Patients with a documented bacterial infection on the day of varix blee

### Outcome definitions

- Primary bacteremia was defined as positive blood cultures without another associated infection and clinical signs of infection after N-butyl-2-cyanoacrylate injection
- Common skin contaminants (*diptheroids*, *Bacillus spp*, *Propionibacterium spp*, coagulase-negative Staphylococci, Aerococcus spp, Micrococcus spp) were counted as contaminants unless blood cultures were positive on two separate occasions or if there were clinical signs of infection
- Recurrent bacteremia was defined as a subsequent episode of bacteremia after the resolution of the first episode occurring  $\geq$ 14 days from the last date of the positive blood culture of the first event
- Persistent bacteremia was defined as at least 5 days of positive blood cultures after implementation of appropriate treatment
- Multidrug-resistant infections were classified as methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant S. aureus, vancomycinresistant Enterococci, extended-spectrum β-lactamase (ESBL) producing Gramnegative bacilli, and Gram-negative bacilli that are resistant to multiple classes of antimicrobial agents

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## Regulte

Table 1. Baseline characteristics						<ul> <li>Table 2. Characteristics of nine patients with recurrent bacteremia after</li> </ul>									
Variable	All patients (n=193)	Primary bacteremia (n=60)	No primary bact eremia (n=123)	P value	endoscoj Patient No.	pic inject	tion of N-	butyl-2 c	yanoacry 4	vlate for k	bleeding gas	tric varices	8	9	
Age (years)	60.0 ± 12.3	59.6 ± 11.3	60.1 ± 12.7	0.78											
Male, n (%)	146 (75.6%)	47 (78.3%)	99 (74.4%)	0.69	Age/sex	F/38	53/M	65/M	60/M	45/M	48/M	83/F	71/M	31/M	
Etiology of liver disease HBV Alcoholic	38 (19.7%) 110 (57.0%)	9 (15.0%) 33 (55.0%)	29 (21.8%) 77 (57.9%)		Cultured organisms	E. coli	E. coli	K. pneumo niae	K. pneumo niae	E. coli	K. pneumoniae	P. e aeruginosa	K. pneumonia	S. eaureus	
HBV+Alcoholic HCV Unknown	8(4.1%) 14 (7.3%) 23 (11.9%)	2 (3.3%) 8 (13.3%) 8 (13.3%)	6 (4.5%) 6 (4.5%) 15 (11.3%)	0.22	Microbiological characteristics	ESBL	ESBL	ESBL	ESBL	ESBL	Cefotaxime- sensitive	Ceftazidime -sensitive	Cefotaxime	- Methicillin -resistant	
Presence of hepatocellular carcinoma	47 (24.4%)	17 (28.3%)	30 (22.6%)	0.49											
Child-Pugh classification A B C	68 (35.2%) 98(50.8.0%) 27(14.0%)	19 (31.7%) 33 (55.0%) 8 (13.3%)	49 (36.8%) 65 (48.9%) 19 (14.3%)	0.72	Episodes of bacteremia meeting study criteria	/ <sup>2</sup>	2	5	2	3	3	2	2	4	
MELD	13.5 ± 5.4	13.7 ± 5.3	13.4 ± 5.4	0.70	Relapse/ Reinfection	Relapse	Relapse	Relapse	Relapse	Relapse	Relapse	Reinfection	Relapse	Relapse	
WBC count (x10 <sup>9</sup> /L)	8.4 ± 4.6	$8.7 \pm 5.0$	8.2 ± 4.4	0.48	later al (dece)	00	40	40	47	47	47	404	05	05	
Hemoglobin (g/dL)	$8.8 \pm 2.1$	$8.9 \pm 1.9$	8.8 ± 2.3	0.92	Interval (days)	68	10	43	1/	1/	47	121	25	25	
Platelet count (x10 <sup>9</sup> /L)	$100.2\pm57.8$	$95.8\pm60.9$	$102.3\pm56.5$	0.47	No. of										
Albumin (g/dL)	$\textbf{2.8} \pm \textbf{0.6}$	$2.9\pm0.5$	$\textbf{2.8}\pm\textbf{0.6}$	0.90	endoscopic 2	2	1	2	3	4	3	1	3	2	
Bilirubin (mg/dL)	$2.4 \pm \ 2.8$	$2.3 \pm \ 2.3$	$2.3\pm~2.7$	0.909	njeeden										
Prothrombin time (INR)	$1.5\pm\ 0.5$	$1.4 \pm 0.3$	$1.5\pm\ 0.5$	0.75	Amount of injected	0.5	4 5	4 5	0.5	0	0.5	0.5	4	4.5	
Creatinine (mg/dL)	$1.1 \pm 0.4$	$1.1 \pm 0.4$	$1.1 \pm 0.4$	0.64	N-butyl-2	2.5	1.5	1.5	3.5	Ζ	2.5	2.5	1	1.5	
Sodium (mEq/L)	$139.2\pm~4.0$	$139.5\pm~4.5$	$139.3\pm~4.2$	0.56	Other										
Systolic BP (mmHg)	110.1 ± 22.5	$111.2\pm21.4$	$109.6\pm23.0$	0.66	underlying condition	DM	DM	DM, Pul TB	DM, IPF	DM	DM, HCC	DM, HCC	DM, HCC	HCC	
Mean injection volume (cc)	1.8 ± 0.8	$1.9\pm1.1$	$1.7\pm0.7$	0.18											
Mean follow-up duration (d ays)	912.1 ± 904.5	$943.3\pm890.4$	$898.0\pm913.8$	0.75	Prognosis	Death	Death	Death	LT	Alive	Death	Transfer	Transfer	LT	
	Table 1. Baseline chara      Variable  Age (years) Male, n (%)  Etiology of liver disease HBV Alcoholic HBV+Alcoholic HCV Unknown  Presence of hepatocellular carcinoma Child-Pugh classification A B C MELD  WBC count (x10 <sup>9</sup> /L) Hemoglobin (g/dL)  Platelet count (x10 <sup>9</sup> /L) Albumin (g/dL)  Platelet count (x10 <sup>9</sup> /L) Albumin (g/dL)  Piothrombin time (INR) Creatinine (mg/dL) Sodium (mEq/L) Systolic BP (mmHg) Mean injection volume (cc) Mean follow-up duration (d ays)	• Table 1. Baseline characteristicsVariableAll patients (n=193)Age (years) $60.0 \pm 12.3$ Male, n (%) $146 (75.6\%)$ Etiology of liver disease HBV $38 (19.7\%)$ Alcoholic $110 (57.0\%)$ HBV+Alcoholic $8(4.1\%)$ HCV $14 (7.3\%)$ Unknown $23 (11.9\%)$ Presence of hepatocellular carcinoma $47 (24.4\%)$ Child-Pugh classification A $68 (35.2\%)$ B $98(50.8.0\%)$ C $27(14.0\%)$ MELD $13.5 \pm 5.4$ WBC count (x10 <sup>9</sup> /L) $8.4 \pm 4.6$ Hemoglobin (g/dL) $8.8 \pm 2.1$ Platelet count (x10 <sup>9</sup> /L) $100.2 \pm 57.8$ Albumin (g/dL) $2.8 \pm 0.6$ Bilirubin (mg/dL) $1.1 \pm 0.4$ Sodium (mEq/L) $139.2 \pm 4.0$ Systolic BP (mmHg) $110.1 \pm 22.5$ Mean injection volume (cc) $1.8 \pm 0.8$ Mean follow-up duration (d ays) $912.1 \pm 904.5$	• Table 1. Baseline characteristics           ·         All patients (n=193)         Primary bacteremia (n=60)           Age (years) $60.0 \pm 12.3$ $59.6 \pm 11.3$ Male, n (%)         146 (75.6%)         47 (78.3%)           Etiology of liver disease HBV         38 (19.7%)         9 (15.0%)           Alcoholic         110 (57.0%)         33 (55.0%)           HBV+Alcoholic         8(4.1%)         2 (3.3%)           HCV         14 (7.3%)         8 (13.3%)           Unknown         23 (11.9%)         8 (13.3%)           Presence of hepatocellular carcinoma         47 (24.4%)         17 (28.3%)           Child-Pugh classification         A         68 (35.2%)         19 (31.7%)           B         98(50.8.0%)         33 (55.0%)         33 (55.0%)           C         27(14.0%)         8 (13.3%)           MELD         13.5 $\pm 5.4$ 13.7 $\pm 5.3$ WBC count (x10 <sup>9</sup> /L)         8.4 $\pm 4.6$ 8.7 $\pm 5.0$ Hemoglobin (g/dL)         2.8 $\pm 0.6$ 2.9 $\pm 0.5$ Bilirubin (mg/dL)         2.4 $\pm 2.8$ 2.3 $\pm 2.3$ Prothrombin time (INR)         1.5 $\pm 0.5$ 1.4 $\pm 0.3$ Creatinine (mg/dL)         1.1 $\pm 0.4$	• Table 1. Baseline characteristics           Variable         All patients (n=193)         Primary bacteremia (n=60)         No primary bacteremia eremia (n=123)           Age (years) $60.0 \pm 12.3$ $59.6 \pm 11.3$ $60.1 \pm 12.7$ Male, n (%)         146 (75.6%)         47 (78.3%) $99$ (74.4%)           Etiology of liver disease HBV $38$ (19.7%) $9$ (15.0%) $29$ (21.8%)           Alcoholic         110 (57.0%)         33 (55.0%)         77 (57.9%)           HBV+Alcoholic $8(4.1\%)$ $2$ (3.3%) $6$ (4.5%)           HCV         14 (7.3%) $8$ (13.3%)         15 (11.3%)           Presence of hepatocellular carcinoma         47 (24.4%)         17 (28.3%) $30$ (22.6%)           Child-Pugh classification         A $68$ (35.2%) $19$ (31.7%) $49$ (36.8%)           B $98(50.8.0\%)$ $33 (55.0\%)$ $65$ (48.9%) $35$ (55.0%) $65$ (48.9%)           C $277(14.0\%)$ $8 (13.3\%)$ 19 (11.3%) $19 (31.7\%)$ $49$ (36.8%)           B $98(50.8.0\%)$ $33 (55.0\%)$ $65$ (48.9%) $64 (4.9\%)$ $7$ (28.3%) $10 (22.6\%)$ C $277(14.0\%)$	• Table 1. 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Characteristics of endoscopic injection of N-result (n=123)         Age (years) $60.0 \pm 12.3$ $59.6 \pm 11.3$ $60.1 \pm 12.7$ $0.78$ Male, n (%)       146 (75.6%)       47 (78.3%)       99 (74.4%) $0.69$ Etiology of liver disease       9 (15.0%)       29 (21.8%)       Cultured organisms       E. coli         HBV       38 (50.0%)       77 (57.9%)       6 (45.5%) $0.22$ Microbiological characteristics       E. sell       E. coli         HCV       14 (7.3%)       8 (13.3%)       16 (45.5%) $0.22$ $0.44$ Microbiological characteristics       E. sell       ESBL       EsBL <td>• Table 1. Baseline characteristics         • Table 2. Characteristics of nine patiends cospic injection of N-butyl-2 cospic injecospic injection of N-butyl-2 cospic injection of N-bu</td> <td>• Table 1. Baseline characteristics         • Table 1. Baseline characteristics         • Table 2. 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Characteristics of nine patients with recurre endoscopic injection of N-butyl-2 cyanoacrylate for I           · Age (years)         <math>60.0 \pm 12.3</math> <math>59.6 \pm 11.3</math> <math>60.1 \pm 12.7</math> <math>0.76</math>           Male, n (%)         146 (75.6%)         477 (78.3%)         99 (74.4%)         <math>0.66</math>           Etology of liver disease         Hev         <math>81(3.3\%)</math> <math>6(4.5\%)</math> <math>0.22</math>           HEV Akcoholic         110 (57.0%)         <math>33 (56.0\%)</math> <math>77 (57.9\%)</math> <math>0.22</math> <math>Cultured organism         <math>E. coli</math> </math></td> <td>Table 1. Baseline characteristics         All patients (n=60)         Primary bacterenia (n=60)         No primary bact previous (n=60)         Primary bact (n=60)</td> <td>• Table 1. Baseline characteristics         • Table 2. 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Characteristics of nine patients with recurrent bacterial after endoscopic injection of N-butyl-2 cyanacorytate for bielding gastric varies           Age (years)         60.0 ± 12.3         59.6 ± 11.3         60.1 ± 12.7         0.78           Male, n (%)         146 (75.6%)         47 (78.3%)         99 (74.4%)         0.69           Etology of liver disease HBW         38 (19.7%)         9 (15.0%)         29 (21.8%)           Alcoholic         10 (16.70%)         23 (3.5.0%)         614.5%)         0.22         Cultured (rganisms         E coli         E. coli         K         R preumo preumo nise         K         P preumonise         P preumonise         R earry preumo sensitive           Child Pugh classification Child Pugh classification A         64 (52.5%)         19 (31.7%)         49 (38.8%)         0.72         5         2         3         2         2           Child Pugh classification Ca         64 (55.2%)         19 (31.7%)         49 (38.8%)         0.72         5         2         3         2         2         2         3         2<td>• Table 1. 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MELD, Model for end-stage liver disease; BP, blood pressure

89 isolates were cultured from 60 patients with primary bacteremia after N-butyl-2-cyanoacrylate injection

- 46 episodes of gram-positive blood stream infection
  - coagulase-negative staphylococci (26.1%), species of Steptococcus (19.6%), Enterococcus faecium (17.4%), Staphylococcus aureus (13.0%), other Enterococcus species (10.9%), and other microorganisms (6.5%)
- 43 episodes of gram-negative blood stream infection
- Escherichia coli (44.2%), Klebsiella pneumoniae (32.6%), Enterobacter cloacae (4.7%), Pseudomonas aeruginosa (4.7%), and other species (14.0%).

The interval is the period between the first bacteremia episode and endoscopic injection of N-butyl-2 cyanoacrylate

The amount of injected N-butyl-2 cyanoacrylate is used for the first endoscopic hemostasis. DM, diabetes mellitus; TB, tuberculosis; HCC, hepatocellular carcinoma; LTCF, long-term care facility; LT, Liver transplantation; Pul TB, pulmonary tuberculosis; IPF, idiopathic pulmonary fibrosis; ESBL, extendedspectrum β-lactamase

In patient 52, Klebsiella pneumoniae caused recurrent bacteremia, and then anaerobic GPC, GPB, and Enterococcus faecalis were identified.

# Conclusion

Recurrent bacteremia occurred in 4.7% of cirrhotic patients following cyanoacrylate injection for the treatment of gastric variceal bleeding. Foreign-body-type infection of the polymerized N-butyl-2cyanoacrylate should be suspected in patients who had received previous endoscopic treatment with N-2-butyl-cyanoacrylate and fails to disclose another source of infection.



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