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Citation

Woittiez, N. J. C., Prehn, J. van, Immerseel, F. van, Goossens, E., Bauer, M. P., Ramspek, C. L., ... Ludikhuize, J. (2022). Toxinotype A *Clostridium perfringens* causing septicaemia with intravascular haemolysis: two cases and review of the literature. *International Journal Of Infectious Diseases*, 115, 224-228. doi:10.1016/j.ijid.2021.12.331

Version: Publisher's Version

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Note: To cite this publication please use the final published version (if applicable).



Toxinotype A *Clostridium perfringens* causing septicaemia with intravascular haemolysis: two cases and review of the literature

N.J.C. Woittiez^a, J. van Prehn^{b,*}, F. van Immerseel^c, E. Goossens^c, M.P. Bauer, PhD^d, C.L. Ramspek^e, R.M.E. Slangen^f, I.M. Purmer^a, J. Ludikhuizen^{a,g}

^a Department of Intensive Care, Haga Teaching Hospital, The Hague, The Netherlands

^b Department of Medical Microbiology, Leiden University Medical Centre, Leiden, The Netherlands

^c Livestock Gut Health Team Ghent, Department of Pathology, Bacteriology and Avian Diseases, Faculty of Veterinary Medicine, Ghent University, Merelbeke, Belgium

^d Department of Acute Internal Medicine, Leiden University Medical Centre, Leiden, The Netherlands

^e Department of Surgery, Haga Teaching Hospital, The Hague, The Netherlands

^f Department of Gastroenterology and Hepatology, Haga Teaching Hospital, The Hague, The Netherlands

^g Section of Acute Medicine, Department of Internal Medicine, VU University Medical Center, Vrije Universiteit, Amsterdam, the Netherlands



ARTICLE INFO

Article history:

Received 24 September 2021

Revised 10 December 2021

Accepted 13 December 2021

Keywords:

Clostridium perfringens

Haemolysis

Mortality

Toxinotyping

Toxinotype A

ABSTRACT

Background: Septicaemia with intravascular haemolysis is a rare, but often fatal, presentation of *Clostridium perfringens* infection. *C. perfringens* is a Gram-positive, anaerobic bacterium that can produce multiple toxins. Toxinotyping is not performed regularly.

Methods: This article describes two human cases of *C. perfringens* infections. Toxinotyping was performed using polymerase chain reaction (PCR). Additionally, a structured review of the literature was performed which searched specifically for cases of *C. perfringens* infection with haemolysis.

Results: Both cases were identified as toxinotype A strains and both cases were fatal. Also, both cases showed marked haemolysis during their clinical course, which is assumed to have played a significant role in their outcome. In total, 83 references were identified describing human *C. perfringens* infection with haemolysis. Mortality rates have been stable over the last 10 years at 80%. Toxinotyping has been performed in a total of six cases. Of the four cases analysed by PCR, all were identified as toxinotype A. **Conclusions:** Haemolytic *C. perfringens* infections are rare but are fatal in most cases. Toxinotyping is performed rarely. The authors advocate increased use of toxinotyping to gain insight into pathophysiology and more effective interventions.

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Introduction

Clostridium perfringens (*C. perfringens*) is a Gram-positive, anaerobic, rod-shaped bacterium which is commonly found in soil, food and intestinal tracts of humans and animals (Kiu and Hall, 2018). *C. perfringens* infections show a broad spectrum of clinical manifestations, including intestinal infections by specific toxinotypes, asymptomatic bacteraemia, gangrene, massive intravascular haemolysis and multi-organ failure from septic shock. Septicaemia with subsequent haemolysis is notorious for rapid clinical

deterioration and death (80% mortality) (Van Bunderen et al., 2010).

C. perfringens can produce a wide array of more than 20 toxins (Kiu and Hall, 2018). The combination of six of these toxins [alpha toxin, beta toxin, epsilon toxin, iota toxin, *C. perfringens* enterotoxin and necrotic enteritis B-like toxin] is used to determine the toxinotype (A to G) (Rood et al., 2018). Based on animal and in-vitro studies, the alpha toxin appears to be the major virulence factor in human *C. perfringens* septicaemia with gas gangrene and haemolysis (Flores-Díaz and Alape-Girón, 2003; Stevens et al., 2012; Kiu and Hall, 2018). However, it is likely that other toxins, such as theta toxins, contribute in disease development (Stevens and Bryant, 2002; Suzaki et al., 2021).

This article describes two fatal cases of toxinotype A *C. perfringens* septicaemia causing massive intravascular haemolysis. In ad-

* Corresponding author. Address: Department of Medical Microbiology (E4), Leiden University Medical Centre, PO Box 9600, 2300 RC Leiden, The Netherlands. Tel.: +31 71 52 61652.

E-mail address: j.vanprehn@lumc.nl (J. van Prehn).

dition, an overview of all published literature (since 1990) from human cases is provided.

Case 1

A 65-year-old male with a history of type 2 diabetes, subclinical hypothyroidism and ischaemic stroke was admitted to the Emergency Department (ED) with a 2-day history of acute abdominal pain. Over the previous 3 weeks, symptoms had included loss of appetite, confusion, vague upper stomach pain and general malaise. On arrival, he was afebrile with an alert mental status and severe abdominal pain. Vital signs were unremarkable, except for tachypnoea (25–30 breaths/min). Physical examination revealed severe diffuse abdominal pain showing signs of peritoneal irritation. Computed tomography (CT) scan showed extensive gas-forming liver abscesses with subcapsular gas, aerobilia with signs of intraperitoneal breakthrough. Broad-spectrum antibiotics (cefuroxime, metronidazole and single-dose tobramycin) were administered, and two hepatic drains were placed (CT-guided). Within the first hour of placement of the drains, 3 L of sanguinolent fluid was drained. Subsequently, the patient developed septic shock with jaundice and haemoglobinuria. Laboratory findings revealed a significant decrease in haemoglobin levels (from 6.8 mmol/L to 0.9 mmol/L within a 6-h interval) caused by massive intravascular haemolysis with metabolic acidosis (pH 6.93, bicarbonate 7 mmol/L, lactic acid 14.9 mmol/L). This raised the suspicion of *C. perfringens* infection, and penicillin and ciprofloxacin (for possible mixed bacterial flora) were added to the antibiotic regime.

The next day, blood and hepatic fluid cultures revealed *C. perfringens*, and the patient was transferred to an academic centre for further management and laparotomy. A necrotic gall bladder and 3 L of abdominal blood were removed. Gangrenous cholecystitis was the source of infection. Despite further antibiotic escalation, the patient died within hours of surgery due to refractory sepsis and multi-organ failure.

Case 2

A 69-year-old male with a history of chronic obstructive pulmonary disease, hypertension and gastrointestinal stromal tumour with liver metastases presented to the ED with a 2-day history of nausea, vomiting, dyspnoea and increasing jaundice. The gastrointestinal stromal tumour had been treated with avapritinib for 6 months with good response. The primary tumour had been resected approximately 15 months prior to presentation, and four remaining liver metastases had been treated with percutaneous microwave ablation 12 days earlier.

On presentation, the patient was tachypnoeic (30 breaths/min) with 88% SpO₂, tachycardic (122 beats/min), and jaundiced with mottling and a prolonged capillary refill time. Blood pressure was 142/82 mmHg. The right upper abdominal quadrant was tender. Ultrasonography showed no evident liver abscess(es), but hyper-echoic speckles in the hepatic veins were observed, suspected to be gas bubbles. Oxygen supplementation, fluid resuscitation and broad-spectrum antibiotics (cefuroxime, gentamicin and metronidazole) were initiated.

Within 1 h of presentation, the patient deteriorated acutely, with decreased consciousness and progressive respiratory failure. This was followed by circulatory arrest due to intermittent asystole and pulseless electric activity. Blood chemistry showed increasing lactic acidosis (16 mmol/L), decreasing haemoglobin level (from 6.5 to 2.1 mmol/L in 2 h despite transfusion) and progressive hyperkalaemia (from 4.9 to 9.0 mmol/L despite treatment). After 2.5 h of cardiopulmonary resuscitation, continuing resuscitation was deemed futile, and the patient died. Additional blood results showed intravascular haemolysis (free haemoglobin 317 µmol/L

and hyperbilirubinaemia of 264 µmol/L), and blood cultures grew *C. perfringens*, *Clostridium ramosum* and *Bacteroides fragilis*.

Methods

Literature review

PubMed was searched on 7 January 2021: (((“haemolysis” [tiab]) OR (“hemolysis” [tiab])) AND (“clostridium perfringens” [tiab])), period 1990–2020. All articles in the English language reporting on human cases (age ≥16 years) with a *C. perfringens* infection and intravascular haemolysis were included.

Toxinotyping

Polymerase chain reaction (PCR) toxinotyping was performed according to the method described by Rood et al. (2018).

Results

The PubMed search returned 138 results, of which 81 references described 83 cases of human *C. perfringens* infection with intravascular haemolysis (Table 1). The mortality rate in published cases appears to have remained unchanged over the past 10 years (30/38: 79%). In two cases, a non-PCR method was used to detect alpha toxin, while in four cases (5%), PCR toxinotyping on various toxins was performed. In the cases analysed by PCR, only the alpha-toxin gene was detected (i.e. toxinotype A). Multiplex PCR toxinotyping of the isolates of Cases 1 and 2 classified both as toxinotype A.

Discussion

Rapid progression to septicaemia and massive intravascular haemolysis is a well-known but rare clinical presentation of *C. perfringens* infection. Intravascular haemolysis is attributed to secretion of alpha toxin and occurs in 7–15% of cases with bacteraemia (van Bunderen, 2010). The approximate doubling time of *C. perfringens* of 7 min and rapid upregulation of toxin production contribute to rapid patient deterioration (McArthur et al., 2006). Median time between admission and death is 8 h (van Bunderen et al., 2010). Immediate appropriate antibiotic treatment and surgical source control are paramount: interventions before onset of massive haemolysis seem to improve survival (Simon et al., 2014). *In vitro*, *C. perfringens* alpha-toxin production and activity can be suppressed within 15–45 min by either clindamycin, metronidazole or rifampin (Stevens et al., 1987). Cornerstones of treatment remain identical to sepsis treatment, namely early recognition and intervention with the specific aim of reducing toxin production (Watt et al., 2012).

The literature reveals a paucity of toxinotyping data in human cases. Including the strains included in this study, six strains have been PCR-typed and all were positive for alpha toxin alone. Alpha toxin is a membrane-disrupting protein which causes cell necrosis by hydrolysing phospholipids in the cell membrane (Kiu and Hall, 2018). Likewise, it causes spherocytosis and haemolysis of erythrocytes (van Bunderen et al., 2010). Furthermore, alpha toxin decreases cardiac contractility, inhibits trafficking of immune cells such as neutrophils to the site of infection, and causes a micro-aerophilic environment by local coagulation and vasoconstriction, all favouring *C. perfringens* overgrowth (Kiu and Hall, 2018). All *C. perfringens* toxinotypes should, in theory, be able to induce intravascular haemolysis, as all types can produce alpha toxin (Kiu and Hall, 2018; Flores-Díaz and Alape-Girón, 2003). However, after extensive literature review, only toxinotype A has been found in human cases with haemolysis to date. The fact that alpha toxin

Table 1
Literature overview of human cases with *Clostridium perfringens* infection and haemolysis.

	Author	Year	Age	Sex	Survival	Origin of infection	Positive culture	Toxin typing	Method of typing	Toxinotype
1	Bätge	1992	61	M	Yes	Liver abscess	Blood	NR	-	-
2	Ifthikaruddin	1992	54	F	No	Unknown	Blood	NR	-	-
3	Hübl	1993	84	F	No	Unknown (intestinal?)	Blood (i)	α toxin (iii)	Turbidimetric assay (serum PLC activity)	-
4	Rogstad	1993	61	M	No	Liver abscess (micro)	Blood, liver, spleen	NR	-	-
5	Clarke	1994	53	F	Yes	Necrotizing enteritis	Blood, peritoneal fluid	NR	-	-
6	Gutiérrez	1995	74	M	No	Liver abscess (micro)	Blood	NR	-	-
7	Meyerhoff	1995	66	F	No	Unknown	Blood	NR	-	-
8	Bush	1996	58	F	Yes	Unknown (post-laparoscopic cholecystectomy)	Blood	NR	-	-
9	Jones	1996	66	F	No	Liver abscess	Blood, liver abscess	NR	-	-
10	Pun	1996	47	M	No	Cholangitis	Blood (i)	NR	-	-
11	Singh	1996	73	F	No	Unknown	Blood	NR	-	-
12	Singer	1997	55	F	No	Unknown	Blood	NR	-	-
13	Alvarez	1999	77	F	No	Abdominal	Blood	NR	-	-
14	Thomas	1999	73	M	Yes	Cholecystitis	Blood (i)	NR	-	-
15	Eckel	2000	65	F	Yes	Liver abscess	Blood (i)	NR	-	-
16	Barrett	2002	NR	F	No	Septic spontaneous abortion	Blood	NR	-	-
17	Halpin	2002	29	F	Yes	Postcaesarean endometritis	Blood	NR	-	-
18	Hamoda	2002	39	F	Yes	Postamniocentesis endometritis	Blood	NR	-	-
19	Jimenez	2002	79	M	No	Unknown	Blood	NR	-	-
20	Kreidl	2002	80	M	No	Liver abscess	Blood, liver abscess	NR	-	-
21	Ikegami	2004	67	M	Yes	Acute pancreatitis	Pancreas	NR	-	-
22	Solis	2004	50	M	No	Hepatic gas gangrene + mycotic aneurysm of dCHA	Donor liver and hepatic artery	NR	-	-
23	Vaiopoulos	2004	74	M	No	Intestinal and biliary	Blood	NR	-	-
24	Au	2005	65	M	No	Liver abscess	NR	NR	-	-
25	Pirrotta	2005	50	M	No	Unknown	Blood and stool	NR	-	-
26	Rodriguez	2005	57	M	No	Biliary	Blood	NR	-	-
27	Daly	2006	80	M	No	Liver abscess	Blood	NR	-	-
28	Eigneberger	2006	60	M	No	Liver abscess	Liver (gram staining)	NR	-	-
29	Kwon	2006	71	F	No	Unknown	Blood (i)	NR	-	-
30	Loran	2006	69	F	No	Liver abscess	NR	NR	-	-
31	McArthur	2006	49	M	No	Abdominal	Blood	NR	-	-
32	Ohtani	2006	78	M	No	Liver abscess	Blood, liver abscess	NR	-	-
33	Kapoor	2007	58	M	No	Unknown	Blood	NR	-	-
34	Poon	2007	64	F	No	Unknown (hepatobiliary?)	Blood (i)	NR	-	-
35	Poulou	2007	74	M	No	Unknown	Blood	Lecithinase (iii)	Turbidity on the egg yolk medium	-
36	Egyed	2008	39	F	Yes	Unknown	Blood	NR	-	-
37	Hess	2008	81	M	No	Acute diverticulitis	Blood, brain, heart, spleen (i)	NR	-	-
38	Nadisauskiene	2008	31	F	No	Postcaesarean endometritis	Blood	NR	-	-
39	Boyd	2009	46	M	No	Acalculous cholecystitis	Blood	NR	-	-
40	Uppal	2009	61	M	No	Unknown	Blood	NR	-	-
41	Bryant	2010	60	F	Yes	Uterus	Blood and intrauterine samples	NR	-	-
42	Bunderen	2010	74	M	Yes	Cholangitis	Blood	NR	-	-
43	Merino	2010	83	F	No	Liver abscess	Blood	NR	-	-
44	Ng	2010	61	F	Yes	Liver abscess	Blood (i)	NR	-	-
45	Rajendran	2010	58	M	Yes	Liver abscess	Blood, liver abscess, gall bladder	NR	-	-
46	Stroumsa	2011	41	F	Yes	Infected uterine myoma	Blood (i)	NR	-	-
47	Law	2012	50	F	No	Liver abscess	Blood	NR	-	-

(continued on next page)

Table 1 (continued)

	Author	Year	Age	Sex	Survival	Origin of infection	Positive culture	Toxin typing	Method of typing	Toxinotype
48	Qandeel	2012	59	M	Yes	Liver abscess (post-laparoscopic cholecystectomy)	Blood	NR	-	-
49	Watt	2012	52	M	Yes	Pan-enteritis	Blood	NR	-	-
50	Cécilia	2013	64	M	No	Unknown	Blood	NR	-	-
51	Dutton	2013	66	M	No	NR	Blood	NR	-	-
52	Okon	2013	71	M	No	Unknown	Blood, CSF (i)	NR	-	-
53	Kitterer	2014	71	M	No	Liver abscess	Blood	NR	-	-
54	Kurasawa	2014	65	M	No	Liver abscess	Blood	NR	-	-
55	Renaudon-Smith	2014	37	M	Yes	Liver abscess	Blood	NR	-	-
56	Simon	2014	79	F	No	Unknown	Blood	NR	-	-
57	Cochrane	2015	65	F	Yes	Emphysematous cholecystitis	Blood	NR	-	-
58	Khan	2015	77	M	No	Cholecystitis/Liver abscess	No (ii)	NR	-	-
59	Li	2015	71	M	Yes	Liver abscess (post-TACE)	Blood	NR	-	-
60	Shindo	2015	73	F	No	Liver abscess	Liver abscess (i)	α toxin	Multiplex PCR (iv)	A
61	Yamaguchi	2015	80–89	F	No	Unknown	Bile, pleural effusions (i)	NR	-	-
62	Carretero	2016	65	M	Yes	Liver abscess	Blood, liver abscess (i)	NR	-	-
63	Hashiba	2016	82	M	No	Liver abscess, emphysematous cholecystitis	Blood	α toxin	Multiplex PCR (v)	A
64	Lim	2016	58	M	No	Liver abscess	Blood	NR	-	-
65	Medrano-Juarez	2016	32	M	Yes	Unknown	Blood (i)	NR	-	-
66	Sarvari	2016	76	F	No	Emphysematous gastritis	Intestinal and subcutaneous tissue	NR	-	-
67	Balan	2017	71	F	No	Unknown	Blood	NR	-	-
68	Ewing	2017	53	F	No	Necrotizing fasciitis right arm	Wound	NR	-	-
69	Kent	2017	74	F	No	Enteritis necroticans (based on symptoms)	Blood	NR	-	-
70	Kukul	2017	17	M	No	Gastrointestinal tract	Quadratus muscle	NR	-	-
71	Gelonch	2018	66	M	No	Liver abscess	NR	NR	-	-
72	Gelonch	2018	63	M	No	Liver abscess	NR	NR	-	-
73	Shibazaki	2018	68	F	No	Liver abscess	Blood	NR	-	-
74	Wild	2018	81	F	No	Unknown	Blood	α toxin	PCR (iv)	A
75	Sakaue	2019	76	M	No	Liver abscess	Blood	α toxin	Multiplex PCR (vi)	A
76	Uojima	2019	83	M	No	Liver abscess (post-TACE)	Liver abscess	NR	-	-
77	Chinen	2020	80	F	No	Liver abscess	Blood, liver abscess (i)	NR	-	-
78	Fujikawa	2020	77	F	No	Liver abscess	Blood	NR	-	-
79	Kawakami	2020	83	M	No	Pelvic abscess	Blood, intra-abdominal samples	NR	-	-
80	Koubaisi	2020	50	M	No	Abdominal?	Blood	NR	-	-
81	Olds	2020	85	F	No	Liver abscess	Blood	NR	-	-
82	Smit	2020	61	M	No	Liver abscess	Blood	NR	-	-
83	Smit	2020	71	F	No	Unknown	Blood (i)	NR	-	-
84	Woittiez	2021	65	M	No	Gangrenous cholecystitis	Blood, liver abscess	α toxin	Multiplex PCR (vii)	A
85	Woittiez	2021	69	M	No	Hepatogenic?	Blood (i)	α toxin	Multiplex PCR (vii)	A

M, male; F, female; positive culture, positive for *C. perfringens*; post-TACE, after transarterial chemo-embolization because of hepatocellular carcinoma; dCHA, donor common hepatic artery; NR, not reported; CSF, cerebrospinal fluid; PLC, phospholipase C; PCR, polymerase chain reaction; (i) multi-microbial, including *C. perfringens*; (ii) Gram-positive anaerobic rods in liver parenchyma; (iii) only alpha toxin/lecithinase was analysed, no other typing toxins; (iv) alpha toxin, beta toxin, epsilon toxin, iota toxin and *C. perfringens* enterotoxin were analysed; (v) as for (iv), plus beta2-toxin; (vi) as for (iv) plus necrotic enteritis B-like toxin and binary enterotoxin of *C. perfringens*; (vii) as for (iv) plus necrotic enteritis B-like toxin.

alone has been found is likely to be the result of testing just a small number of (typing) toxins in a small number of strains. Considering the known wide array of toxins and virulence factors which *C. perfringens* can produce, it would be shortsighted to conclude that alpha toxins alone play a virulent role. Thus, a complete overview of the possible pathogenic role of other toxinotypes and their toxins is lacking. Toxinotyping of future cases could re-

veal whether human haemolytic *C. perfringens* septicemia is indeed caused solely by type A strains.

Conclusion

Current treatment strategies are ineffective or initiated too late for most patients with haemolytic *C. perfringens* septicemia. As

the alpha-toxin storm is the biggest driving force behind deterioration, the authors advocate the need to investigate supplemental treatment approaches in a toxin-specific way [e.g. antiserum (Goossens et al., 2016) or nanobodies that target haemolytic activity]. Improved attention to determination and reporting of *C. perfringens* toxins and toxinotypes may provide more insight into the role of these toxins and virulence factors in pathophysiology, and could subsequently reveal new targets for intervention.

Conflict of interest statement

None declared.

Funding

None.

Ethical approval

Not required.

Author contributions

Study design: NW, JP and JL.

Data collection: NW, JP, FI, EG, MB, CR, RS, IP and JL.

Data analysis and writing: NW, JP, FI, EG and JL.

All authors reviewed the manuscript and approved the final manuscript.

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