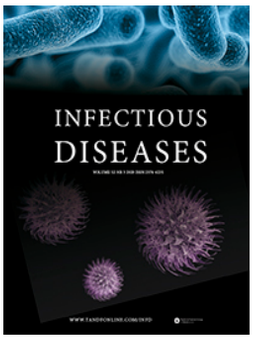

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ORIGINAL ARTICLE

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The antibiotic susceptibility pattern of gas gangrene-forming *Clostridium* spp. clinical isolates from South-Eastern Hungary

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ABSTRACT

Introduction: *Clostridium perfringens* and other gas gangrene-forming clostridia are commensals of the human gut and vaginal microbiota, but can cause serious or even fatal infections. As there are relatively few published studies on antibiotic susceptibility of these bacteria, we decided to perform a 10-year retrospective study in a South-Eastern Hungarian clinical centre.

Methods: A total of 372 gas gangrene-forming *Clostridium* spp. were isolated from clinically relevant samples and identified with rapid ID 32A (bioMérieux, France) and MALDI-TOF MS (Bruker Daltinics, Germany) methods. Antibiotic susceptibility was determined with E-tests.

Results: We identified 313 *C. perfringens*, 20 *C. septicum*, 10 *C. sordellii*, 10 *C. sporogenes*, 9 *C. tertium*, 6 *C. bifermentans*, 4 *C. histolyticum* isolates. In *C. perfringens* isolates, the rate of penicillin resistance was 2.6% and the rate of clindamycin resistance 3.8%. Penicillin resistance was found in 6.8% and clindamycin resistance in 8.5% of the non-perfringens *Clostridium* spp. isolates.

Conclusion: The antibiotic susceptibility of *C. perfringens* isolates was in good agreement with previous publications. The rates of resistance to penicillin and clindamycin were very low. The resistance rates of non-perfringens *Clostridium* spp. isolates were higher than those of *C. perfringens* strains, but lower than those published in the literature.

KEYWORDS
Clostridium spp.
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Instruction

C. perfringens and other gas gangrene-forming *Clostridium* species (*C. bifermentans, C. soredellii, C. sporogenes, C. novyi, C. histolyticum, C. tertium*) are gram-positive, spore-forming, obligately anaerobic rods. They are found in the gut and vaginal microbiota and are widely distributed in the environment [1,2]. *C. perfringens* can cause gas gangrene, food poisoning (especially *via* the type A strains), necrotizing enteritis (especially *via* the type C strains) and fatal enterotoxinemia [3–5]. Gas gangrene (myonecrosis) is usually caused by *C. perfringens* (approximately 80% of all cases), *C. novyi*, *C. septicum*, followed by *C. histolyticum, C. sordelli, C. bifermentans* and *C. sporogenes* [6]. Guedira *et al.* reported rare manifestations of *C. perfringens* infection, such as panophthalmitis and orbital cellulitis; however, emphysematous gastritis can also be caused by *C. perfringens* [7,8]. An outbreak of necrotizing fasciitis caused by *C. sordelli* was reported among nine black-tar heroin users in California in 2004 with four fatalities [9]. *C. sordellii* may be associated with tissue inflammatory response, severe hypotension, shock, endometritis, fulminant toxic shock syndrome, arthritis, pericarditis and pleuropneumonia [10–14]. *C. septicum* has been reported to cause emphysematous aortitis, sepsis with meningitis, colon carcinoma and hematological malignancies [15–17] and *C. bifermentans* was cultured from empyema [18].

Antibiotic resistance is an important topic not only among aerobic, but also among anaerobic bacteria. A high rate of resistance to some antibiotics has been reported for members of the *Bacteroides fragilis* group [19] and multidrug resistant strains (MDR) have been isolated in the last years [20,21]. In the literature, there is little information on the antibiotic resistance of *Clostridium* spp. We performed a retrospective study with the aim of collecting and analysing antibiotic susceptibility of gas gangrene-forming *Clostridium* spp. over a 10-year period in the South-Eastern region of Hungary.

Materials and methods

Sample collection, culture and identification of bacterial isolates

For anaerobic culture, we accepted the aspirated specimens from normally sterile body sites. BacT/ALERT (bioMérieux, Marcy-l'Étoile, France) anaerobic blood culture bottles were used. The skin surface was scrubbed with 70% ethanol from the centre outward in concentric circles, followed by iodine for 30 s or a minute, and iodine was then removed with alcohol. Only samples from deep or surgical wounds were accepted for anaerobic culture. Samples were taken by needle aspiration or a small amount of tissue removed after decontamination. Abscesses were aspirated with a sterile syringe, and aspirates were injected into anaerobic transport vials (Port-A-Cul, Beckton-Dickinson, Franklin Lakes, NJ, USA) or air was removed and syringes closed with a steril needle. Swab samples were not accepted from oral or gingival abscesses. The area of the abscess was isolated with cotton rolls and dried with sterile cotton swabs, povidon-iodine or chlorhexidine applied for disinfection and the content of the abscess was aspirated. Fluid specimens could be submitted in sterile tightly capped leak-proof containers. The samples were sent immediately to the laboratory [22].

C. perfringens and other gas gangrene-forming clostridia isolates were isolated from clinically relevant samples in patients - one positive culture per patient - treated in the Clinical Centre of the University of Szeged, Hungary, during the period of 1 January 2008 to 31 December 2017. Cultures were performed in liquid enrichment broth for aerobic (bouillon with glucose) and anaerob bacteria (chopped meat broth, which was boiled and cooled before use) and on solid agar plates. Samples were cultured on Schaedler anaerobic blood agar (bioMérieux, Marcy-l'Étoile, France), vancomycin-kanamycin laked blood agar and egg yolk agar for 48 h, at 37 °C in an anaerobic chamber (Perkin Elmer, Waltham, MA, USA) under anaerobic conditions (85% N_2, 10% CO_2, 5% H_2). Bacteria isolated between 1 January 2008 and 31 December 2012, were identified using the rapid ID 32A (bioMérieux, Marcy-l'Étoile, France) method. To detect activity of preformed enzymes, strips were incubated under aerobic conditions for 4 h at 37 °C. The biochemical profile was analysed by computer with an up-to-date, specific database (analytic profile index, version 3.2) provided by the manufacturer. The reliable, species-level identification was accepted when the agreement of the profile with the database was $\geq$95%. For quality control, *C. perfringens* ATCC 13,124 *C. sporogenes* ATCC 19,404 *C. bifermentans* ATCC 638, *C. tertium* ATCC 14,573 *C. sordellii* ATCC 9714, *C. histolyticum* ATCC 19,401 *C. septicum* ATCC 12,464 were used.

Identification of isolates between 1 January 2013 and 31 December 2017, was performed with Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS) (Bruker Daltonik, Bremen, Germany) using Biotyper Version 3.0 software at the species level. High confidence identification (species level

identification) was accepted when the log score value of the isolate was ≥2.000.

Antbiotic susceptibility testing

Antibiotic susceptibility tests were performed immediately after isolation, strains were not stored in a cryobank. The minimal inhibitory concentration (MIC) values of different antibiotics were determined with the E-test method (Liofilchem s. r. l., Roseto degli Abruzzi, Italy) at the time of isolation. The antibiotics tested were penicillin, amoxicillin/clavulanic acid, cefoxitin, imipenem, meropenem, clindamycin, metronidazole and, for *C. perfringens,* tigecycline as well. Interpretation of the MIC-values was done according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (penicillin, amoxicillin/clavulanic acid, imipenem, meropenem, clindamycin, metronidazole) or to the Clinical and Laboratory Standards Institute (CLSI) (cefoxitin) [23,24]. As tigecycline breakpoints for *Clostridium* spp. have not yet been established by either EUCAST or CLSI, the breakpoints of the US Food and Drug Administration (FDA) were applied [25].

Statistical evaluation

The data, obtained from our local microbiological data base, was analysed using a linear regression test in the SigmaPlot 12.3 package, and significance was defined as $p < .05$. The antibiotic susceptibility data was analysed with the chi-squared test (χ^2-test) using the SigmaPlot 12.3 package.

The study was approved by the Ethical Committee of University of Szeged (No.: 4361), according to the Helsinki Declaration (1975) and its revision (2002).

Results

Bacterial isolates

A total of 372 clinically relevant gas gangrene-forming *Clostridium* isolates (313 *C. perfringens*, 20 *C. septicum*, 10 *C. sordellii*, 10 *C. sporogenes*, 9 *C. tertium*, 6 *C. bifermentans*, 4 *C. histolyticum*) were cultured during the 10-year period. Patients had an average age of 65.0 years (0.2–93 years) and 51.6% were female, 48.4% were male. The number of isolates per year displayed an increasing trend from 2008 to 2017 ($r = 0.771$) (Figure 1). Isolates emanated from patients treated in surgery (37.1%), internal medicine (24.7%), the emergency department (8.9%), various intensive care units (ICUs) (6.5%), and from patients treated in other departments (Table 1). Bacteria were isolated either as a single pathogen in

Table 1. Distribution of the clinical departments or units where the samples were collected.

Clinical departments/units	No. of strains (%)
Surgery	138 (37.1)
Internal Medicine	92 (24.7)
Emergency Department	33 (8.9)
Traumatology	31 (8.3)
Intensive Care Units	24 (6.5)
Dermatology	24 (6.5)
Pediatrics	9 (2.4)
Obstetrics and Gynaecology	3 (0.8)
Neurosurgery	3 (0.8)
Other clinics*	15 (4,0)
Total	372 (100)

*Other clinical departments or units involved in this study: Otorhinolaryngology, Orthopaedics, Pathology, Neurology, Maxillofacial surgery, Psychiatry, Urology, Opththalmolgy, Oncotherapy.

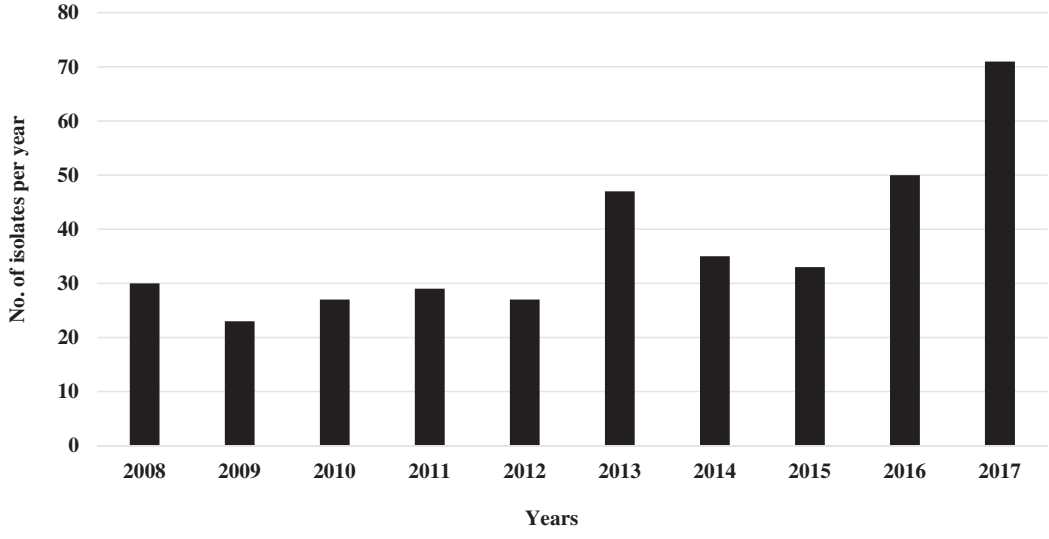

Figure 1. Number of gas gangrene-forming clostridia isolates in the ten years of the study.

pure culture (21.5%) or in mixed culture (78.5%). Besides blood (14.8%), the most common sample types were wound (20.7%), bile (20.2%), abscess (14.8%), surgical samples (15.0%) and intraabdominal fluid (6.7%) (Table 2). Six clinical samples (four from wounds and two from bile) yielded *C. perfringens* together with a non-perfringens *Clostridium* spp. (Table 3). The *Clostridium* spp. isolates were two *C. sporogenes*, two *C. bifermentans*, and two *C. sordellii*. There was no relation between the patients and no suspicion of an outbreak in the different wards or units. Forty-three *C. perfingens,* and 12 non-perfringens *Clostridia* (five *C. septicum*, three *C. sordellii*, two *C. tertium*, one *C. bifermentans* and one *C. sporogenes*) were isolated from blood cultures.

Table 2. Distribution of sample types from which gas gangrene-forming clostridia were isolated during 2008–2017.

Sample types	No. of sample types (%)
Wound	77 (20.7)
Bile	75 (20.2)
Surgical samples	56 (15.0)
Blood culture	55 (14.8)
Abscess	55 (14.8)
Intraabdominal fluid	25 (6.7)
Other types*	29 (7.8)
Total	372 (100)

*Other sample types were: biopsy, bronchoalveolar lavage (BAL), skin bulla, duodenum, gastric sample, middle ear, liver puncture, pancreas cyst puncture, pleural puncture, lacrimal sample, conjunctiva, pancreas cyst, nasal sample.

Antibiotic susceptibility

Antimicrobial susceptibility, MIC_{50} and MIC_{90} values and MIC ranges are summarized in Tables 4 and 5. All isolates were susceptible to amoxicillin/clavulanic acid, cefoxitin, meropenem, imipenem and all *C. perfringens* isolates were susceptible to tigecycline. The rates of penicillin and clindamycin resistance were low (penicillin: *C. perfringens* 2.6%, non-perfringens clostridia 6.8%; clindamycin: *C. perfringens* 3.8%, non-perfrigens clostridia 8.5%) (Tables 4 and 5). The number of penicillin and clindamycin resistant isolates did not increase during

Table 3. Samples that contained two different gas gangrene-forming *Clostridium* species.

Laboratory code	Sample type	Clinical department/unit	Species 1	Species 2
8928 (2012)	Wound	Surgery	*C. perfringens*	*C. sporogenes*
52,329 (2012)	Wound	ICUs	*C. perfringens*	*C. bifermentans*
29,140 (2016)	Wound	Surgery	*C. perfringens*	*C. sordellii*
103,059 (2016)	Bile	Internal Medicine	*C. perfringens*	*C. sporogenes*
53,024 (2017)	Wound	Traumatology	*C. perfringens*	*C. sordellii*
102,554 (2017)	Bile	Internal Medicine	*C. perfringens*	*C. bifermentans*

ICUs: Intensive Care Units.

Table 4. Antibiotic susceptibility of *C. perfringens* isolates.

	MIC (mg/l)			Percentage (%)		
Antimicrobial agents	Range	MIC_{50}	MIC_{90}	Susceptible	Intermediate	Resistant
Penicillin	0.002–2	0.064	0.25	95.5	1.9	2.6
Amoxicillin/clavulanic acid	0.008–3	0.032	0.125	100	0	0
Cefoxitin	0.016–8	0.5	2	100	0	0
Meropenem	0.002–1	0.016	0.125	100	0	0
Imipenem	0.002–2	0.125	0.5	100	0	0
Clindamycin	0.016–≥256	0.5	4	96.2	0	3.8
Metronidazole	0.016–3	1.5	4	100	0	0
Tigecycline	0.016–2	0.25	2	100	0	0

MIC: Minimal Inhibitory Concentration.
MIC_{50}: MIC that inhibits the growth of 50% of the bacteria.
MIC_{90}: MIC that inhibits the growth of 90% of the bacteria.

Table 5. Antibiotic susceptibility of non-perfringens gas gangrene-forming *Clostridium* spp. isolates.

	MIC (mg/l)			Percentage (%)		
Antimicrobial agents	Range	MIC_{50}	MIC_{90}	Susceptible	Intermediate	Resistant
Penicillin	0.002–2	0.064	0.25	91.5	1.7	6.8
Amoxicillin/clavulanic acid	0.002–0.75	0.047	0.5	100	0	0
Cefoxitin	0.047–4	0.25	2	100	0	0
Meropenem	0.008–0.19	0.023	0.064	100	0	0
Imipenem	0.002–4	0.047	0.19	100	0	0
Clindamycin	0.008–256	0.25	4	91.5	0	8.5
Metronidazole	0.008–4	1	4	100	0	0

MIC: Minimal Inhibitory Concentration.
MIC_{50}: MIC that inhibits the growth of 50% of the bacteria.
MIC_{90}: MIC that inhibits the growth of 90% of the bacteria.

the study period. Eight *C. perfringens* and four *C. tertium* were resistant to penicillin. Twelve *C. perfringens*, two *C. tertium*, two *C. sporogenes* and one *C. septicum* were resistant to clindamycin. There were no significant differences in resistance to penicillin and clindamycin between perfringens and non-perfringens isolates ($p = .2$ and .22, respectively).

Discussion

A limitation of our study is the scarce information about the correctness of the sampling technique, to avoid contamination by normal flora, possible oxygene exposition and the speed of transportation to the laboratory.

Although *C. perfringens* and other gas gangrene-forming *Clostridium* species are part of the human gut and vaginal microbiota, they can cause serious and sometimes fatal infections. Only a few published up-to-date studies are found on the antibiotic susceptibility of clinical strains. Our general aim was to perform a regional retrospective study on the distribution of different species, sample types, and wards where patients were treated and on antibiotic susceptibility. We investigated 372 isolates and most (84.1%) were *C. perfringens*, while 15.9% were non-perfringens gas gangrene-forming *Clostridium* species. We found that amoxicillin/clavulanic acid, cefoxitin, imipenem, meropenem and metronidazole had excellent activity against these isolates as had tigecyclin against *C. perfringens*. Only a few of them were resistant to penicillin and clindamycin. We compared our results with a Slovenian study by Jeverica *et al.* [26], who tested 44 *C. perfringens* strains and found no resistante to penicillin, amoxicillin/clavulanic acid, imipenem, meropenem and metronidazole and only 7% were resistant to clindamycin. Wang *et al.* [27] reported from Northern Taiwan that three (6%) of 50 *C. perfringens* strains were resistant to clindamycin, and all were susceptible to penicillin, amoxicillin/clavulanic acid, ampicillin/sulbactam, imipenem, meropenem, metronidazole and tigecycline. Our antibiotic susceptibility findings were similar to those published in the literature. Wang *et al.* [27] investigated 43 non-perfringens clostridial strains, including *C. bifermentans* ($n = 7$), *C. sporogenes* ($n = 3$), *C. histolyticum* ($n = 2$), *C. septicum* ($n = 2$), *C. sordellii* ($n = 2$). They found that 16.3% were resistant to penicillin and 27.3% to clindamycin, and all were susceptible to amoxicillin/clavulanic acid, ampicillin/sulbactam, imipenem, meropenem, tigecycline and metronidazole. Marchand-Austin *et al.* [28] investigated 289 non-perfringens gas gangrene-forming *Clostridium* strains from Ontario, Canada, and found that 14.2% were resistant to penicillin, 8% to cefoxitin, 21.6% to clindamycin and none to meropenem and metronidazole. Interestingly, no strain was resistant to cefoxitin. Of non-perfringens *Clostridium sp.* isolates, four *C. tertium* were resistant to penicillin, and two *C. tertium*, two *C. sporogenes* and one *C. septicum* were resistant to clindamycin. Chew *et al.* [17] reported that *C. septicum* was associated with some malignancies which made us realise that isolation of *C. septicum* may indicate to malignancy. Of our isolates, two were *C. septicum,* one from a patient with carcinoma of the pancreas are from a patient with carcinoma of an eyelid. We found no patient with carcinoma of the colon.

Conclusion

The excessive use of antibiotics has led to selection of antibiotic resistant bacteria, especially among the aerobes. As antibiotic susceptibility data of gas gangrene-forming *Clostridium* strains is quite limited, a survey on this topic was undertaken. The rates of resistance to penicillin and clindamycin of *C. perfringens* isolates were very low. The resistance rates of non-perfringens *Clostridium* spp. isolates were lower than those published in the literature, but higher than those of our *C. perfringens* isolates. There was no increasing tendency in the prevalence of resistant isolates per year.

Disclosure statement

No potential conflict of interest was reported by the authors.

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