Nontoxigenic Highly Pathogenic Clone of Corynebacterium diphtheriae, Poland, 2004–2012

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Twenty-five cases of nontoxigenic Corynebacterium diphtheriae infection were recorded in Poland during 2004–2012, of which 18 were invasive. Alcoholism, homelessness, hepatic cirrhosis, and dental caries were predisposing factors for infection. However, for 17% of cases, no concomitant diseases or predisposing factors were found.

Corynebacterium diphtheriae is the causative agent of diphtheria. Its toxin is considered the major virulence factor. Since introduction of vaccine against the diphtheria toxin in the 1940s, infections caused by toxigenic corynebacteria have been well controlled in industrialized countries that have high coverage rates of childhood vaccination with 3 doses of diphtheria-tetanus-pertussis vaccine (T). Nevertheless, emergence of nontoxigenic C. diphtheriae infections has been reported in some of these countries.

In line with other European countries, Poland routinely vaccinates against diphtheria (online Technical Appendix, wwwnc.cdc.gov/EID/article/19/11-0297-Techapp1.pdf). According to data from the World Health Organization, >95% of children in Poland are fully vaccinated against diphtheria. The last diphtheria case was recorded there in 2000 (www.who.int/immunization_monitoring/data/incidence_series.xls).

The absence of diphtheria during the past 13 years suggests that the high vaccination coverage rates in Poland protect against diphtheria. In 2004, the first case of sepsis caused by nontoxigenic C. diphtheriae was reported (2). Other cases were recorded in 2006, and since 2007, several cases of C. diphtheriae invasive infections have been recorded every year (Table 1). In addition, local infections—usually wound infections—caused by nontoxigenic C. diphtheriae were recorded (Table 2). A total of 25 nontoxigenic C. diphtheriae infections were recorded in Poland in 2004–2012, of which 18 were invasive infections.

The Study

All patients were admitted to local hospitals and clinical samples for microbiological investigations were sent to the nearest laboratories. C. diphtheriae isolates were sent to National Institute of Public Health–National Institute of Hygiene for confirmation and toxigenicity testing, biotyping, pulsed-field gel electrophoresis (PFGE), multilocus sequence typing (MLST), and ribotyping. Case classification and microbiological methods used are presented in the online Technical Appendix. Data collected for epidemiologic analysis included location; type of infection; year of presentation; and patient age, sex, concomitant diseases, socioeconomic status, and intravenous drug use (IVDU).

All isolates from local and invasive infections were identified as biotype gravis, except for the isolate from patient Loc-05, which was identified as biotype mitis. All 25 isolates were characterized by PFGE, and 20 isolates (18 from invasive and 2 from local infections) were characterized by MLST (3–5). All the isolates except the mitis isolate belonged to the same pulsotype revealed by PFGE. All the isolates characterized by MLST belonged to genotype sequence type 8. Eight of the isolates (5 from invasive and 3 from local infections) also were genotyped by using ribotyping. All 8 isolates showed indistinguishable ribotype patterns (3).

All but 1 invasive infection were identified in male patients, whereas local infections affected male and female patients similarly. Age groups of patients most affected by invasive infections were 31–40 years, followed by 51–60 years; for local infections, persons 51–60 years of age were mostly affected (Figure). Patients’ ages ranged from 17 to 71 years. The cases occurred in various parts of Poland; no epidemiologic links were identified.

Epidemiologic data analysis revealed that predisposing factors of nontoxigenic C. diphtheriae invasive infections were related to conditions associated with low socioeconomic status, such as alcoholism, homelessness, and dental caries, as well as to hepatic cirrhosis. For 3 (17%) patients (Inv-08, Inv-09, Inv-13), no concomitant diseases or predisposing factors were identified. These were healthy men aged 17, 24, and 37 years of age, respectively. Predisposing factors for local infections were not analyzed. The sources of all infections described in the study were not identified. Despite IVDU being regarded as a risk factor for C. diphtheriae invasive infection, none of the patients were intravenous drug users.

Conclusions

Diphtheria is a rare disease in Europe. In 2006–2009 only 150 cases were reported in European Union and European Economic Area/European Free Trade Association countries. Most of the cases (114 cases) occurred in Latvia, where diphtheria is endemic. The other diphtheria cases.
C. diphtheriae circulating in Poland or infections. This raises a valid question: is C. diphtheriae been documented in any countries reporting nontoxigenic country over a 9-year period. This phenomenon has not clone despite isolation of the strains in different part of the –, 105 from local infections in Italy and the United Kingdom, biotype dominated among the invasive isolates in Switzerland sive infections belonged to biotype 108, 5 of age (, respectively, originated from patients <15 years of age (, other hand, in Italy and the United Kingdom, 70% and 13% of invasive infections were diagnosed in children. On the other hand, in Poland, persons most affected were 31–40 years and 51–60 years of age, whereas in other countries most patients were younger (up to 34 years of age). No C. diphtheriae infections among children were recorded in Poland, whereas in France, almost 20% of invasive infections were diagnosed in children. On the other hand, in Italy and the United Kingdom, 70% and 13% of isolates, respectively, originated from patients <15 years of age (5,8,10).

In Poland, all but 1 strain isolated from local and invasive infections belonged to biotype gravis, whereas biotype mitis dominated among the invasive isolates in Switzerland and France, and biotype gravis dominated among isolates from local infections in Italy and the United Kingdom (5,8–10). All but 1 isolate from Poland represent a single clone despite isolation of the strains in different part of the country over a 9-year period. This phenomenon has not been documented in any countries reporting nontoxigenic C. diphtheriae infections. This raises a valid question: is a single clone of C. diphtheriae circulating in Poland or does the identified clone have increased pathogenic properties? This question remains unanswered because the carrier state of C. diphtheriae has not been examined in the Polish population.

Taking these data and the literature review into consideration, C. diphtheriae infections frequently are associated with endocarditis. Muttaiyah et al. (11) and Mishra et al. (12) demonstrated that most patients with C. diphtheriae endocarditis have underlying cardiac disease, prosthetic valves, or a history of IVDU. This finding, however, was not observed among patients in Poland.

The portal of entry for invasive nontoxigenic C. diphtheriae infection has not been fully elucidated. However, some authors shown that skin lesions are the most likely sources (9,13,14). In the cases presented here, skin ulceration was uncommon (1 case), but dental caries were found in >22% of cases. Dental caries could be a portal of entry.

The main limitation of this work is lack of complete data. Nevertheless, nontoxigenic C. diphtheriae can be concluded to be an emerging pathogen in Poland and has

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### Table 1. Cases of bloodstream infections caused by nontoxigenic Corynebacterium diphtheriae, Poland, 2004–2012

| Patient | Age, y/sex | Concomitant disease | Location | Year | Additional information |
|---------|------------|---------------------|----------|------|------------------------|
| Inv-01  | 38/M       | Dental caries        | Warsaw   | 2004 | Endocarditis diagnosed |
| Inv-02  | ND/M       | ND                  | Bydgoszcz| 2006 | Homeless               |
| Inv-03  | 51/M       | HIV suspected        | Bydgoszcz| 2007 |                        |
| Inv-04  | 37/M       | Dental caries        | Gdynia   | 2007 |                        |
| Inv-05  | 53/M       | Alcoholism, hepatic cirrhosis | Rzeszów | 2008 |                        |
| Inv-06  | 50/F       | Portal and posthepatitic C cirrhosis, dental caries | Bydgoszcz | 2008 |                        |
| Inv-07  | 32/M       | Alcoholism, abscess of the liver | Gdynia | 2008 |                        |
| Inv-08  | 24/M       | Not identified       | Gdynia   | 2009 |                        |
| Inv-09  | 17/M       | Not identified       | Kraków   | 2009 |                        |
| Inv-10  | 60/M       | Alcoholism           | Sosnowiec| 2009 |                        |
| Inv-11  | 60/M       | Dental caries, frostbite of feet | Bydgoszcz | 2010 | Homeless               |
| Inv-12  | 36/M       | Alcoholism, delirium | Gdynia   | 2010 |                        |
| Inv-13  | 37/M       | Not identified       | Legnica  | 2010 | Endocarditis diagnosed |
| Inv-14  | ND/M       | ND                  | Sosnowiec| 2011 |                        |
| Inv-15  | 50/M       | Skull trauma, skin ulceration | Radom | 2011 | Homeless               |
| Inv-16  | 71/M       | Stroke               | Kraków   | 2011 |                        |
| Inv-17  | 65/M       | Hepatic cirrhosis, encephalopathy, diabetes mellitus | Gdansk | 2012 |                        |
| Inv-18  | ND/M       | Stroke               | Poznań   | 2012 | Endocarditis diagnosed |

ND, no data.

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### Table 2. Local infections caused by nontoxigenic Corynebacterium diphtheriae, Poland, 2004–2012

| Patient | Age, y/sex | Location | Year | Site of C. diphtheriae isolation |
|---------|------------|----------|------|---------------------------------|
| Loc-01  | ND/M       | Bydgoszcz| 2007 | Wound                          |
| Loc-02  | 29/F       | Warszawa | 2007 | Fistula                         |
| Loc-03  | ND/M       | Bydgoszcz| 2007 | Wound                          |
| Loc-04  | 51/M       | Warszawa | 2008 | Wound                          |
| Loc-05  | 61/F       | Bydgoszcz| 2010 | Shank cyst                      |
| Loc-06  | 56/F       | Gdynia   | 2010 | Wound                          |
| Loc-07  | 59/M       | Warszawa | 2012 | Wound                          |

ND, no data.

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Figure. Number of nontoxigenic Corynebacterium diphtheriae infections, Poland, 2004–2012. Excluded are 5 cases for which no data were available.
the potential to cause serious infections. The number of nontoxicogenic \textit{C. diphtheriae} infections might be higher because reporting of only toxigenic \textit{C. diphtheriae} infections is mandatory in Poland. Moreover, in clinical settings, detection of coryneform bacteria in blood cultures is often dismissed as contamination, and in severe cases of the disease, \textit{C. diphtheriae} might never be identified as the etiologic agent of bloodstream infection.

Homelessness, alcohol abuse, IVDU, and diabetes mellitus were mentioned in the literature as risk factors for \textit{C. diphtheriae} invasive infections. In the cases presented here, 31\% of patients were homeless, and 22\% reported alcohol dependency but only 1 patient had diabetes mellitus. No patients reported IVDU. In 17\% of cases, hepatic cirrhosis was ascertained, which suggests that it also may be another predisposing factor to infection. Moreover, dental caries is a highly probable portal of entry of \textit{C. diphtheriae} invasive infection and has not been documented by other authors. However, such infections also might occur in persons with no identified predisposing factors.

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