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NOTES

Cutaneous Diphtheria in the Urban Poor Population of Vancouver, British Columbia, Canada: a 10-Year Review▽

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Between 1998 and 2007, records from 33 patients with cutaneous diphtheria from Vancouver's inner city were reviewed. Cases were associated with injection drug use and poverty. Coinfections with *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Arcanobacterium haemolyticum* occurred. *Corynebacterium diphtheriae* is endemic in Vancouver's urban core, with strains of multilocus sequence type (MLST) 76 predominating.

Corynebacterium diphtheriae is a reemerging pathogen (11). It is endemic in many developing countries and has been associated with outbreaks in developed countries (19). Cutaneous diphtheria is characterized by a chronic, nonhealing ulcer, often a source for persistent colonization (6). It has the potential to cause systemic disease and may be an important reservoir for ongoing transmission within a susceptible population (23).

In Vancouver, Canada, a susceptible population exists in the "downtown eastside" (DTES), which represents a poor inner-city community with high rates of injection drug use, HIV infection, and homelessness (3, 25, 28). Outbreaks of *C. diphtheriae* have been previously reported in this community (5, 23). Thus, a clinical, microbiological, and molecular review of cutaneous diphtheria patients presenting to St. Paul's Hospital, Vancouver, Canada, was conducted.

Cutaneous diphtheria was defined as a chronic ulcer growing *C. diphtheriae* from a wound specimen. From 1998 to 2007, a systematic chart review was completed for cases identified by retrospectively reviewing the laboratory information system at St. Paul's Hospital. Ethics approval was obtained for this study.

Microbiological methods were conducted as previously described by Romney et al. (23). Briefly, Gram-positive bacilli consistent with *C. diphtheriae* were subcultured on Tinsdale medium and identified using the API Coryne strip (bioMérieux, Durham, NC). *C. diphtheriae* isolates were routinely sent to the British Columbia Centre for Disease Control and the National Microbiology Laboratory for confirmation with starch fermentation/utilization tests and cellular fatty acid composition analyses (1). Diphtheria toxin studies were carried out using the modified Elek test (10) and PCR (9, 21). Multilocus sequence typing (MLST) was performed as described by Bolt et al. (2), as follows: extracted DNA was amplified by PCR targeting of 7 *C. diphtheriae* housekeeping loci (*atpA*, *dnaE*, *dnaK*, *fusA*, *leuA*, *odhA*, and *rpoB*). Allelic numbers were assigned to each locus, creating a unique numerical profile, and the sequences were compared with *C. diphtheriae* sequences posted at http://pubmlst.org/cdiphtheriae/.

Other bacterial isolates listed in Table 1 were identified by conventional and automated microbiological methods. Methicillin-resistant *Staphylococcus aureus* (MRSA) was confirmed by penicillin-binding protein 2a detection or PCR for *mecA* and *nuc* if necessary (7).

For the period 1998 to 2007, *C. diphtheriae* was isolated from cultures of wounds of 37 patients. Charts were available for 33 of the 37 patients identified (ages 16 to 78 years; mean, 41.7 years). Basic demographic information and medical and social histories of the patients are listed in Table 2. Patients suffered from multiple medical problems, and only 5/33 patients had no significant medical history. All were residents of the DTES except for 3 individuals, one of whom frequented sex trade workers in this community. Twenty-two patients (66.7%) were known injection drug users, using primarily cocaine and/or heroin.

Wound cultures were polymicrobial, except for one from which only *C. diphtheriae* was isolated. Table 1 lists the other organisms isolated from the wounds. Treatment of cutaneous diphtheria was variable and include the following: antibiotics (all antibiotics [21/33, 63.6%], penicillin G [11/20], cephalosporin [6/20], vancomycin [3/20], or clindamycin [1/20]), surgical debridement (2/33, 6.1%), conservative management/wound care (4/33, 12.1%), not treated (3/33, 9.1%), and not documented (4/33, 12.1%). Compliance rates are generally poor in this patient population, and follow-up was not available.

All isolates studied were nontoxigenic. Molecular investigation by MLST revealed a predominant isolate, sequence type

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TABLE 1. Organisms cultured from wound specimens positive for *C. diphtheriae*

Organism	No. (%) of isolates[a]
Group A *Streptococcus*	21 (63.6)
Group G *Streptococcus*	2 (6.1)
Staphylococcus aureus	18 (54.6)
Methicillin-resistant *Staphylococcus aureus*	3 (9.1)
Coagulase-negative staphylococci	4 (12.1)
Enterococcus faecalis	2 (6.1)
Peptostreptococcus species	1 (3.0)
Arcanobacterium haemolyticum	6 (18.2)
Coliforms	3 (9.1)
Morganella morganii	1 (3.1)
Alcaligenes species	1 (3.1)

[a] $n = 33$.

TABLE 2. Basic demographic information of patients with wound cultures positive for *C. diphtheriae*

Parameter	No. (%) of patients[a]
Gender	
Male	20 (60.1)
Female	13 (39.9)
Ethnicity	
Caucasian	16 (48.5)
Aboriginal	14 (42.4)
Asian	2 (6.1)
Unknown	1 (3.0)
Residence	
Downtown eastside	30 (90.9)
Non-downtown eastside	3 (9.1)
Medical history	
HIV	11 (33.3)
Hepatitis B	6 (18.2)
Hepatitis C	21 (63.4)
Infective endocarditis	9 (27.2)
Diabetes mellitus	3 (9.1)
Recurrent ulcers	8 (24.2)
Venous insufficiency	3 (9.1)
Psychiatric history	7 (21.1)
Substance/social history	
Alcohol (>14 drinks per week)	12 (36.4)
Smoking	25 (75.8)
Sex trade worker	3 (9.1)
Drug use	22 (66.7)

[a] $n = 33$.

76 (ST76) (20/29, 69%). The remaining isolates were distributed among ST5 (1/29), ST32 (6/29), ST78 (1/29), and ST81 (1/29). Four samples were not typed. ST32 was *C. diphtheriae* biotype gravis, while the remaining were *C. diphtheriae* biotype mitis strains.

Over a 10-year period, 33 cases of cutaneous diphtheria were reviewed, with the majority (31/33) closely associated with the DTES. The most common associated conditions involved preexisting comorbidities (hepatitis C) and social circumstances (residence in an impoverished area and injection drug use). Studies in other developed countries have made similar associations (14, 15, 22). In the DTES, rates of HIV and hepatitis C virus (HCV) infections among injection drug users are high, estimated at 17% and 88%, respectively (27, 29). Injection drug use (52%) is also prevalent (4). While the study population characteristics are expected, given the primary residence of the cases, it is important to recognize pockets in urban settings where cutaneous diphtheria is endemic. This report may underestimate its prevalence, as data were captured for only those who sought medical attention.

Both toxigenic and nontoxigenic strains have been observed in cutaneous diphtheria (8, 15). Colonization may serve as a reservoir for potentially invasive disease (13). Studies examining injection drug users and impoverished patients from Switzerland and France revealed clones of nontoxigenic *C. diphtheriae* biotype mitis resulting in bacteremia and endocarditis (14, 22). Septic arthritis has also been reported (16). Skin colonization/infection progressing to invasive disease had been observed in Vancouver, where 7 patients developed bacteremia (1 progressing to infective endocarditis). Nontoxigenic *C. diphtheriae* biotype mitis ribotype Tunisia was cultured in 6/7 cases (23). In this study, biotype mitis strains (23/29, 79.3%) again predominated in this community.

Ribotyping had previously been the gold standard for molecular characterization (12), but systematically augmented databases have become increasingly difficult to access. MLST was developed in the 1990s and has been used for typing of numerous bacterial species (18). With Internet-based methods to compare data typed using a standardized protocol, MLST may prove useful for the subtyping of *C. diphtheriae* strains internationally (2). In this study, the predominant sequence type was 76, which is associated with nontoxigenic strains of biotype mitis. This was not found among the collection of international isolates studied by Bolt et al. (2) and so, geographically, may be restricted to Canada. A comparison to other Canadian strains is currently limited, but such a study is under way (K. Bernard, personal communication). ST5 has been recovered in Russia and the United States, ST32 has been found in Poland and Kazakhstan, and ST81 has not been described to date. None of the strains associated with outbreaks in Eastern Europe and Central America were isolated in Vancouver (2).

Consistent with previous reports, cultures were predominantly polymicrobial, with *Staphylococcus aureus* and *Streptococcus pyogenes* being the most common copathogens (8). MRSA was cultured in 9.1% of wounds, an unexpected finding as 43% of culture-positive wounds from DTES residents harbored MRSA (17). Increasing numbers of wounds coinfected with MRSA may be expected in the future given such high carriage rates. In addition, *Arcanobacterium haemolyticum* has been found to be frequently cocultured (23). *A. haemolyticum*, associated primarily with pharyngeal infections, has been reported in cases of polymicrobial skin and soft tissue infections and, rarely, systemic manifestations (24). No patients in this review were found to have systemic infections with *A. haemolyticum*.

Clinical toxin-mediated diphtheria is rare due to routine childhood immunization in Canada, which was implemented in 1930 (20). However, nontoxigenic *C. diphtheriae* continues to circulate in the DTES. Penicillin or erythromycin is considered the first-line treatment of nontoxigenic cutaneous diphtheria (26), and most patients in this review were treated with penicillin G.

There is a need for increased awareness of the potential for

severe disease in cutaneous diphtheria. Continued laboratory surveillance within the DTES is required, as well as a comparison of isolates (and MLST) from across Canada. Although the current data suggest a predominant strain, the epidemiology of *C. diphtheriae* in the DTES may change in the future, as in the experience in Seattle (15), or remain stable, as described in Europe (14, 22). Based on this 10-year study, molecular and clinical data suggest that *C. diphtheriae* has become endemic in downtown Vancouver.

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