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## EMERGENCE OF *NEISSERIA GONORRHOEAE* STRAINS WITH DECREASED SUSCEPTIBILITY TO CIPROFLOXACIN — QUEBEC, 1994-1995

### Introduction

In 1987, the *Laboratoire de santé publique du Québec* (LSPQ) implemented a surveillance program to monitor the prevalence of penicillinase-producing strains of *Neisseria gonorrhoeae* (PPNG) in the province of Quebec. This voluntary program involved 131 laboratories that participated by sending all their PPNG strains and reporting the number of *N. gonorrhoeae* isolates observed in their laboratories each month. In the early 1990s, following the emergence of gonococcal strains that exhibited increased in vitro resistance to fluoroquinolones in Canada<sup>(1)</sup>, the surveillance program was extended to all strains of *N. gonorrhoeae* for which decreased susceptibilities to antimicrobial agents were detected. (The LSPQ receives about 45% of all gonococcal strains isolated in the province). Between March 1994 and February 1995, we identified, for the first time, four non-PPNG strains showing a decreased susceptibility to ciprofloxacin. This report describes the clinical and epidemiologic features of the patients from whom these strains were isolated as well as the antimicrobial susceptibilities, the auxotype/serovar (A/S), and the plasmid content of the strains.

### Methods:

Susceptibility testing was performed using the agar dilution method in accordance with the procedures recommended by the National Committee for Clinical Laboratory Standards (NCCLS)<sup>(2,3)</sup>. The following antimicrobial agents were used: penicillin (0.032 to 32 µg/mL), tetracycline (0.064 to 32 µg/mL), spectinomycin (8 to 128 µg/mL), ceftriaxone (0.001 to 0.5 µg/mL), and ciprofloxacin (0.0005 to 0.5 µg/mL). GC agar base (BBL) enriched with 1% defined supplement<sup>(2)</sup> was used for all antimicrobial agents. *N. gonorrhoeae* ATCC 49226 and three other

*N. gonorrhoeae* strains — F-28, F-45 and 76.061782 — were used as control strains<sup>(2,4,5)</sup>. Plates were incubated in a 5% to 7% CO<sub>2</sub> atmosphere at 35° C for 20 to 24 hours. Results were interpreted according to the NCCLS<sup>(3)</sup>.

Isolates were further characterized by A/S and plasmid content as previously described<sup>(6-8)</sup>. Requirements for proline, citrulline, ornithine, arginine, uracil, hypoxanthine, leucine, and methionine were determined.

### Results:

Strains were isolated from one woman and three men, ranging in age from 25 to 40 years; all were residents of the Montreal region (Table 1). The woman had been hospitalized for endometritis and pelvic peritonitis; the strain was isolated from her endocervix. The three men presented with urethritis; strains were isolated from the urethra.

According to information collected by the local public health department, Cases 1 and 3 (Table 1) appear to have been infected in southeast Asia. Case 3 had had a casual sexual contact in Thailand prior to symptom onset. Case 1 attributed her infection to the insertion of an intrauterine device while in China. Cases 2 and 4 acquired their infection in Montreal; both had contacts with unidentified casual female partners. Case 2 was born in China but had not travelled outside Canada prior to onset of symptoms. He denied sexual contact with a person residing outside the country.

Based on clinical outcomes only, two patients (Cases 2 and 3) were successfully treated with a fluoroquinolone. The other two cases, treated either with doxycycline alone (Case 4) or with cefoxitin followed by doxycycline plus amoxicillin (Case 1), were treatment failures. Secondary treatments of these two patients with



ofloxacin plus ceftriaxone and ceftriaxone plus doxycycline, respectively, were successful.

All strains were chromosomally resistant to penicillin and tetracycline, and had decreased susceptibility to ciprofloxacin (Table 2). They were susceptible to spectinomycin and ceftriaxone, and all the strains were  $\beta$ -lactamase negative, as determined by the chromogenic cephalosprin method (nitrocefin-based tests). Characterization of the strains by A/S class showed that they belonged to three different classes. All isolates harboured the cryptic plasmid [2.6 megadaltons (Mda)] and two isolates also carried the 24.5 Mda conjugative plasmid.

## Discussion:

Strains of *N. gonorrhoeae* with decreased susceptibilities to the quinolone drugs have previously been reported in Canada<sup>(1,9)</sup>. However, to our knowledge, this is the first report of such isolates in the province of Quebec.

Based on phenotypic characteristics of the strains and clinical features of the patients, it seems that all cases were unrelated. Two of the four cases had a direct association with southeast Asia. The

problem of decreased susceptibility of *N. gonorrhoeae* to quinolone antibiotics among persons acquiring their infection in Asia has been described previously<sup>(1,5,10,11)</sup>. The other two cases were not apparently linked to travel outside Canada but no information was available on sex partners who might have recently travelled or been visiting from outside Canada.

In this report, none of the four cases were treated with regimens as recommended in the *Canadian Guidelines for the Prevention, Diagnosis, Management and Treatment of Sexually Transmitted Diseases in Neonates, Children, Adolescents and Adults*<sup>(12)</sup>. Case 1 was initially treated with 1 g of cefoxitin followed by doxycycline plus amoxicillin. Cases 2 and 3 were treated with a 7-day regimen of quinolones (successful even if the strains had decreased susceptibility to ciprofloxacin), and Case 4 was initially treated with doxycycline alone.

The present recommendations for the treatment of uncomplicated gonorrhea include single-dose regimens of ceftriaxone, cefixime, ciprofloxacin or ofloxacin (plus doxycycline for coinfection with chlamydial infections)<sup>(12)</sup>. We believe that the data reported here do not justify any change in these recommendations at the present time. However, they emphasize

the need for reference laboratories to closely monitor antimicrobial resistance of *N. gonorrhoeae* isolates. In order to reduce secondary transmission and spread of resistant strains, physicians should advise their patients to return for re-evaluation if symptoms persist, especially if a quinolone has been prescribed. A specimen should then be collected for culture and susceptibility testing<sup>(11,13)</sup>.

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Table 1  
Characteristics of the Patients with *N. gonorrhoeae* Isolates Exhibiting Decreased Susceptibilities to Ciprofloxacin, Quebec, 1994-1995

Case # (sex of patient)	Age	Date of Symptoms Onset	Infection Acquired in	Initial Treatment	Clinical Outcome	Subsequent Treatment	Post-Treatment Culture
1 (F)	25	March '94	China	Cefoxitin 1 g i.v. q 8h x 3 days followed by Doxycycline 100 mg bid x 7 days Amoxicillin 500 mg tid x 7 days	Failure	Ofloxacin 400 mg p.o. Ceftriaxone 500 mg i.m. <sup>a</sup>	Negative
2 (M)	28	May '94	Canada (Montreal)	Ofloxacin 400 mg bid x 7 days	Cured	Nil	Not done
3 (M)	33	December '94	Thailand	Ciprofloxacin 500 mg tid x 7 days	Cured	Nil	Not done
4 (M)	40	January '95	Canada (Montreal)	Doxycycline 100 mg bid x 15 days	Failure	Doxycycline 100 mg bid x 15 days Ceftriaxone 250 mg i.m.	Negative

<sup>a</sup> Ceftriaxone was given 3 weeks later.

Table 2  
Antimicrobial Susceptibilities, Plasmid Content and A/S Class of *N. gonorrhoeae* Isolates, Quebec, 1994-1995

Strain No.	Minimum Inhibitory Concentration ( $\mu$ g/mL)					Plasmid Content (Mda)	A/S Class <sup>b</sup>
	Pen <sup>a</sup>	Tet	Spec	Ceft	Cip		
1	4	2	16	0.06	0.5	2.6, 24.5	P/IB-1
2	2	2	32	0.03	0.5	2.6, 24.5	P/IB-8
3	2	2	16	0.03	0.25	2.6	NR/IB-1
4	1	2	16	0.03	0.25	2.6	NR/IB-1

<sup>a</sup> Pen, penicillin; Tet, tetracycline; Spec, spectinomycin; Ceft, ceftriaxone; Cip, ciprofloxacin.

<sup>b</sup> P, proline requiring; NR, no requirement.

the technicians in microbiology laboratories in Quebec who sent the gonococcal strains.

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## Addendum:

In August and September 1995, the LSPQ received, for the first time, two isolates of *N. gonorrhoeae* resistant to ciprofloxacin (MIC = 4 µg/mL). Both strains were isolated from the urethra of a 22-year-old man who appears to have been infected while travelling in the Philippines. Both isolates (from the patient's first and second visits) were β-lactamase positive, resistant to penicillin (MIC ≥ 32 µg/mL) and tetracycline (MIC = 2 µg/mL) but susceptible to spectinomycin (MIC = 16 µg/mL) and ceftriaxone (MIC = 0.016 µg/mL). These isolates belonged to the A/S class NR/IB-3 and carried 2.6, 4.5, and 24.5 Mda plasmids. The patient was initially treated with ofloxacin, 400 mg orally in a single dose, plus doxycycline, 100 mg orally twice a day for 10 days. Because this treatment was unsuccessful, the patient was treated again with cefixime, 800 mg orally in a single dose. To our knowledge, this is the first treatment failure of an uncomplicated gonococcal infection with quinolones reported in Canada.

## Editorial Comment

The 1995 Update of the *Canadian Guidelines for the Prevention, Diagnosis, Management and Treatment of Sexually Transmitted Diseases in Neonates, Children, Adolescents and Adults* has replaced the 1992 edition\*. Nine chapters of the 1992 edition were revised, including those on gonococcal and chlamydial infections. For gonorrhea, the drugs of choice have remained the same but, for some, the dose levels have been reduced.

The 1995 Update recommends **ceftriaxone (125 mg IM in a single dose), OR cefixime (400 mg orally in a single dose), OR** one of the fluoroquinolones, **ciprofloxacin (500 mg orally in a single dose) OR ofloxacin (400 mg orally in a single dose)** as preferred therapy for uncomplicated gonococcal infection in adolescents and adults. These therapies are recommended because of the increased prevalence of gonococcal isolates that are resistant to penicillin and tetracycline. **Spectinomycin (2 g IM in a single dose)** is recommended as an alternative therapy. Ampicillin/amoxicillin is no longer recommended as an alternative therapy as it was in the 1992 edition. All treatment regimens for gonorrhea should be followed by an antimicrobial effective against *Chlamydia trachomatis*, either **doxycycline (100 mg orally x 2/day for 7 days), OR azithromycin (1 g orally in a single dose)**. **Azithromycin is not recommended for non-gonococcal/non-chlamydial urethritis or cervicitis.**

The 1995 Update also recommends that ciprofloxacin or ofloxacin should not be used to treat uncomplicated gonococcal infection if there is a possibility that the infection was acquired in southeast Asia, especially the Philippines. If either ciprofloxacin or ofloxacin is used to treat such cases, a test-of-cure is recommended.

In jurisdictions such as British Columbia, which have a large population of tourists and immigrants from southeast Asia, the

\* Copies are available from the Canadian Medical Association (CMA). Price per copy is \$24.56 (including shipping and handling). Contact Membership Services, CMA, 1867 Alta Vista Drive, Ottawa, Ontario K1G 3Y6, tel: 1-800-267-9703, ext. 2307 (outside Ottawa), or 731-9331, ext. 2307 (Ottawa and area) or Fax: (613) 731-1779.

drugs of first choice for the treatment of uncomplicated gonorrhea are cefixime and ceftriaxone<sup>(1)</sup>.

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## VANCOMYCIN-RESISTANT ENTEROCOCCI ON A RENAL WARD IN AN ONTARIO HOSPITAL

### Introduction:

Vancomycin-resistant enterococci (VRE) are important emerging pathogens. Their inherent resistance to most antimicrobials used in hospitals, including resistance to all licensed antibiotics in Canada, their hardiness in the environment, and their ability to colonize both patients and staff, who can act as continuous reservoirs for their spread, make them ideal nosocomial agents<sup>(1,2)</sup>. Although VRE usually cause infections in only the most compromised hosts, a much higher proportion of the patient population may be colonized. VRE were first reported in Europe in 1988 and were later reported in the United States<sup>(3,4)</sup>. Currently, enterococci account for about 11% of all nosocomial infections in the U.S.<sup>(5)</sup>, but the percentage of enterococcal infections due to VRE has increased from 0.3% to 7.9% between 1989 and 1993<sup>(6)</sup>.

Although a few sporadic cases of VRE had been reported in Canada previously, during August and September of 1995 the first Canadian outbreak was documented after two patients on the renal ward of The Toronto Hospital yielded growth of VRE from screening urine cultures. Active surveillance identified additional VRE-positive patients. The following is a brief report of the outbreak investigation.

### Background:

In August 1995, VRE was isolated from the urine of a 29-year-old woman with systemic lupus erythematosus, an inpatient on the renal ward of a two-site 1,200 bed tertiary care hospital in Toronto, Ontario. Approximately 1 month later, another patient on the same ward yielded a positive urine culture for VRE. These were the first isolates of VRE from the institution following 2 years of active periodic microbiologic surveillance of all urinary isolates of enterococci and prompted active surveillance of patients, staff and the environment by the Infection Control team. On 27 September 1995, the Field Epidemiology Training Program at LCDC was requested to assist in the investigation of the outbreak. A case-control study was also undertaken to identify potential risk factors associated with acquiring VRE.

### Methods:

The target population of the surveillance screening included all renal-ward inpatients, and all hemodialysis patients and their hospital contacts. Perirectal swabs, stool cultures, urine, wound, and/or exit site swabs, as appropriate, were collected to screen for VRE. In addition, 140 environmental cultures were obtained from the renal ward (call bells, telephones, bedrails, toilet seats, floors, counter tops, sink areas, curtains, computer keyboards, commode chairs, and electronic thermometers) and the hemodialysis unit (including beds, EKG monitors, floors, bathroom areas, and curtains). Staff screening (hand and perirectal) was performed on a voluntary basis.

After reviewing the charts of the initial 25 VRE patients, we recognized that the majority had been admitted to one particular wing, Module One, of the renal ward. A case-control study was conducted on this wing to identify potential risk factors associated with acquiring VRE. Cases were defined as having a positive rectal or perirectal swab for VRE (*E. faecium*) > 72 hours after any hospital admission between 1 July and 30 September 1995, and must have stayed on the wing during this time period. Controls were culture-negative for VRE 72 hours after a hospital admission between 1 July and 7 October 1995, and also had to have stayed on the same wing during this time period.

A standardized questionnaire was used to collect data from patient charts, ward-staff interviews, and laboratory records. Data included patient demographics, medical history, hospital history (including transfers and length of stay), medication history, as well as questions focussing on the degree of illness. Data analysis was performed using EpiInfo 6.03 (Centers for Disease Control and Prevention, Atlanta, Georgia). We report the maximum likelihood estimates and exact 95% confidence interval of the odds ratio.

Laboratory confirmation of VRE was performed (for the first 2 months) using Bacto Enterococci confirmatory agar (Difco), a sodium azide-containing selective medium to which vancomycin 6 mg/L was added. During the following 2 months, Bacto m Enterococci agar with 6 mg/L vancomycin was used. Plates were incubated for up to 72 hours at 35° C. A positive isolate was presumed to be a vancomycin-resistant enterococcus species if the isolate was gram-positive, catalase-negative, bile esculin-positive, and PYR-positive. Vancomycin resistance was confirmed by vancomycin agar screen with 6 mg/L vancomycin, incubated for up to 48 hours at 35° C. Susceptibility testing using MicroScan Walkaway System (Micro, Sacramento, CA) was performed. In addition, vancomycin minimal inhibitory concentrations (MICs) using the National Committee for Clinical Laboratory Standards microbroth dilution method were performed (courtesy of D. Low, B. Willey, Toronto). Pulsed-field gel electrophoresis was performed with *Sma*I as the digesting enzyme using conventional techniques. Polymerase chain reaction (PCR) genotyping was performed (C. Rourke, Toronto) with primers for Van A, B, and C (supplied courtesy of G. Tyrell, Halifax).

### Results:

Between 1 July and 17 November 1995, 41 patients were found to be colonized and one patient was infected with vancomycin-resistant *E. faecium*. Thirty-nine (95%) of the patients were receiving dialysis and two were contacts. The mean age was 63 years (range: 29-90) and 30 (71%) were either bedridden or had limited activity. Twenty (48%) of the patients had diarrhea and nine of these tested positive for *C. difficile* toxin. Forty (98%) of the patients had received at least one antibiotic, 29 (70%) had

received multiple ( $\geq 2$ ) antibiotics but only 17 (40%) had received vancomycin.

Nineteen cases and 34 controls were included in the case-control analysis. Cases were more likely to have had longer hospital stays ( $> 10$  days) (OR = 5.78 exact 95% CI: 1.08 59.5); longer stays in Module One ( $> 17$  days) (OR = 5.16; CI: 1.29 23.6); received peritoneal dialysis (OR = 7.62; CI: 1.89 35.3), recently used more than two antibiotics (OR = 16.58; CI: 2.84 182); had diarrhea (OR = 6.18; CI: 1.47 29.9) and/or fecal incontinence (OR =  $\infty$ ; CI: 6.53  $\infty$ ) while in hospital and multiple ( $> 3$ ) hospital admissions in the past year (OR = 4.39; CI: 1.15 19.5). Factors previously described in the literature as associated with colonization or infection (vancomycin use or proximity to the index case) were not associated with acquiring VRE in this population.

Of the 52 renal-ward staff members who worked between 22 July and 4 August 1995, eight (15%) volunteered to be swabbed and none yielded positive cultures for VRE. Of the 140 environmental samples, 10 yielded positive cultures. Sampling included bathroom areas, bed rails, and bedside call bells. In total, four call bells yielded positive cultures for the epidemic strain of VRE. A separate call bell experiment was performed on cracked and broken bells, some of which had visible accumulation of presumed fecal material within the cracks. Despite exterior surface cleaning with a phenolic solution, viable VRE were identified on one call bell after 2 weeks.

All positive cultures from patients and the environment were identified as sorbitol-positive, vancomycin-resistant, ampicillin-resistant, teicoplanin-sensitive *E. faecium*. MICs to vancomycin varied between 4 to 128 mg/L (32% with an MIC  $\leq 8$  mg/L). Pulsed-field gel electrophoresis revealed that all clinical and environmental isolates (with one exception) were closely related, with  $\leq$  two bands difference. This strain, which has been designated The Toronto Hospital "A" strain, may be unique to Toronto. PCR genotyping confirmed that this strain is a Van B-containing *E. faecium*.

## Discussion:

Infection control practices established following the recognition of the first two cases included the use of single rooms and cohorting of colonized patients, temporary closure of the affected unit to new admissions, use of gown and gloves at room entry, use of dedicated thermometers, sphygmomanometers and other medical equipment, and the provision of handwashing facilities and solutions for patients, staff and visitors. Extensive environmental cleaning was conducted, and additional housekeeping staff were utilized. All damaged call bells were removed and replaced. Education of staff, patients, and visitors was provided through in-services, newsletters and notices. Recommendations for the prudent use of vancomycin and for the judicious use of antibiotics were provided for the medical staff. Over the ensuing months, colonized patients were either discharged or re-integrated with the general hospital population with isolation used for patients with poor hygiene or diarrhea. These measures appeared successful and no additional outbreaks have occurred within the hospital.

Public concern was intense during this outbreak. The arrival of VRE in Canada sparked the initiation of a National VRE Point Prevalence Survey conducted as a collaborative effort between the Canadian Hospital Epidemiology Committee (CHEC) and LCDC

during January and February 1996<sup>(7)</sup>. This survey included the participation of 27 hospitals nationwide, targeting "high-risk" populations (surgical, medical, and perinatal ICUs; transplant and oncology patients; and dialysis patients).

This initial outbreak, the preliminary findings of the National VRE Point Prevalence Survey and the re-integration approach used in the hospital following the outbreak have prompted a review of existing protocols for the identification and the infection control management of VRE-positive patients.

This analysis of the first Canadian outbreak of VRE has confirmed some of the risk factors previously reported in the literature. It also recognizes the call bell as a potential and unique vector for ongoing transmission.

Although VRE is endemic in many hospitals in the U.S., its bold appearance in Canada has served as a wake-up call to the Canadian infection control community, who now must determine how to best monitor and manage the potential threat posed by this organism.

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## Editorial Comment

Increased reports of VRE incidence and outbreaks in U.S. hospitals prompted the Canadian Nosocomial Infection Surveillance Program (CNISP), which consists of CHEC and LCDC, to survey 20 health-care facilities throughout Canada regarding their VRE experience. Survey results reported a significant increase in vancomycin use over time and four health-care facilities identified colonized and infected cases of VRE. Surveillance activities for VRE already existed within 63% of the health-care facilities surveyed; however, these surveillance methods were not uniform between or within the health-care facilities. Based on information collected during the outbreak of

VRE in Toronto and this survey, CNISP developed a VRE point prevalence surveillance project, which was implemented in January and February 1996. The point prevalence project used standardized epidemiology data collection and laboratory methods. Screening for VRE was performed among “high-risk” patients including those on medical, surgical and neonatal intensive care units, hemo-oncology and solid organ transplant wards, and those receiving dialysis. Epidemiologic information collected included

patient demographics, admission and specimen collection dates, and use of antibiotics including vancomycin. Laboratory typing and strain identification is to be performed on all positive isolates of VRE and on selected vancomycin-sensitive strains. Preliminary results of the VRE point prevalence surveillance project are pending and will be published in an upcoming CCDD edition. Development of an ongoing surveillance program for VRE is one of the priorities for the CNISP group.

## Preliminary Report

### INVASIVE INFECTION DUE TO *STREPTOCOCCUS INIAE*: A NEW OR PREVIOUSLY UNRECOGNIZED DISEASE — ONTARIO, 1995-1996<sup>(1)</sup>

Between December 1995 and February 1996, four cases of a bacteremic illness, three accompanied by cellulitis and the fourth with infective endocarditis, meningitis, and probable septic arthritis, were identified at Scarborough Grace Hospital, in Scarborough, Ontario. *Streptococcus iniae*, a major fish pathogen<sup>(2-4)</sup> not previously reported as a cause of illness in humans, was isolated from all patients. All four patients were of Chinese descent and had contact with whole, fresh fish purchased locally. This preliminary report describes the clinical cases to date and the possible implications.

#### Case 1:

On 15 December 1995, a 64-year-old female punctured the skin on the dorsum of her right hand with a fish bone while cleaning fresh tilapia (*Oreochromis* sp). About 16 hours later she presented to the Emergency Department (ED) with fever, and diffuse swelling and erythema over the hand. She was previously healthy, aside from medication-controlled hypertension.

On examination, her temperature was 38.5° C, pulse 100 beats per minute, and blood pressure 100/78 mm Hg. There was cellulitis over the dorsum of the hand with lymphangitis. Her leukocyte count was 12.9 x 10<sup>9</sup>/L with a left shift.

She was admitted to hospital and treated with intravenous penicillin and cloxacillin. The cellulitis improved gradually over the next 3 days and she was discharged home after 3 days in hospital on cephalexin to complete 10 days of therapy. Two of three blood cultures, from samples taken on admission, grew a streptococcal species, later confirmed to be *Streptococcus iniae*. Symptoms have fully resolved.

#### Case 2:

On 18 December, a 74-year-old female presented to the ED with pain and swelling over the medial side of her left hand. Three days previously she had lacerated the skin over her left fifth digit with a knife which had just been used to cut and clean an unknown type of fresh fish. Pain and erythema began the day before admission and progressed rapidly. She was previously healthy with no known significant medical illness.

She appeared toxic with a temperature of 38.3° C. The fourth and fifth digits were swollen, hot, and red. Cellulitis with poorly defined borders had spread proximally to the wrist. Lymphangitis was present.

Her leukocyte count was 16.1 x 10<sup>9</sup>/L with 56% neutrophils and her hemoglobin was 148 g/L. She was admitted to hospital and received clindamycin intravenously for 2 days. She was discharged on penicillin V to complete 10 days of therapy. Four of six blood cultures (three aerobic and one anaerobic) grew *S. iniae*. She recovered completely.

#### Case 3:

On 20 December, a 40-year-old female was admitted to hospital with pain, swelling, and cellulitis over her left fourth digit. While scaling a fresh tilapia 18 hours previously, she had punctured the back of this digit with the dorsal fin of the fish. She had a prior history of rheumatic heart disease and thyroiditis.

Her temperature was 38.0° C. Cellulitis was localised over the fourth digit. Lymphangitis was present. Her leukocyte count on admission was 16.9 x 10<sup>9</sup>/L with 82% neutrophils. Antibiotic treatment included intravenous penicillin and clindamycin, followed by oral doxycycline. After 3 days in hospital she was discharged on oral penicillin for 10 days. Two of three blood cultures grew *S. iniae*.

Skin over the site of the cellulitis desquamated after about 7 to 10 days. Mild swelling, pain, and restricted movement at the distal interphalangeal joint have persisted. She is currently undergoing investigations to rule out the possibility of osteomyelitis.

#### Case 4:

On 1 February 1996, a 77-year-old male was brought by ambulance to the same ED with a history of increasing pain in his right knee pain for one week, fever, dyspnea, and confusion. He had been having intermittent sweats and fever. As a hobby he enjoyed cooking, especially fish. About 10 days prior to admission he had prepared a fresh tilapia. It is not known if he had injured himself, but there was no history of cellulitis.

He had a history of diabetes, hypertension, rheumatic heart disease, chronic renal failure, atrial fibrillation, Paget's disease of his right hemipelvis, and osteoarthritis involving his spine and knees. With the increasing knee pain, he had been treated as an outpatient with a non-steroidal anti-inflammatory agent without improvement.

In the ED, he was confused and dyspneic. His temperature was 35.6° C and his respiratory rate was 20. The right knee had a large

effusion and was warm but with no overlying cellulitis. Cardiac examination revealed evidence of aortic insufficiency and mitral regurgitation. While undergoing tests in the ED, he had a res piratory arrest and needed to be intubated.

He was started on empiric cefuroxime and erythromycin because of a questionable left lower lobe pulmonary infiltrate. His leukocyte count was  $25.2 \times 10^9/L$  with 95% neutrophils. A knee aspirate and lumbar puncture were performed 10 hours later. The joint fluid showed a leukocyte count of  $72,000/\mu L$  without evidence of crystals. Cerebrospinal fluid had a leukocyte count of  $87 \times 10^6/L$  with 54% neutrophils, a glucose of 0.8 mmol/L, and a protein of 3.2 g/L ( $n < 0.4$  g/L). Cultures of both fluids were negative. A transesophageal echocardiogram revealed mild aortic insufficiency, moderate mitral regurgitation and a 0.3 cm mobile echogenic mass on the atrial side of the mitral valve.

Both blood cultures from samples taken on admission grew *S. iniae*. He was treated with intravenous penicillin, ceftriaxone, and imipenem for endocarditis.

## Discussion:

All four patients had been preparing fresh, whole fish, three of which were known to be tilapia, from different Scarborough markets. In two cases (Cases 1 and 3) fish were taken live from holding tanks.

Tilapia is a freshwater fin fish. It is reported to be the fastest growing aquaculture crop in the United States and around the world. It is marketed mainly as whole fish. With intensive aquaculture, streptococcal infections are becoming increasingly important in saltwater and freshwater species. In Israel, disease related to a streptococcal infection appeared for the first time in the summer of 1984. A wide range of fish including trout, tilapia, and ornamental fish were affected. The mortality in affected fishponds ranged between 30% and 50%<sup>(3)</sup>. Two species, *S. shiloi* and *S. diffcile*, were isolated from diseased fish. *S. iniae* appears to be closely related to, or the same as, *S. shiloi*. *S. iniae* has not been identified before as causing illness in humans. It has been reported to cause subcutaneous abscesses in Amazon freshwater dolphins<sup>(5,6)</sup> and meningoencephalitis in rainbow trout, coho salmon, and tilapia<sup>(4)</sup>.

Patient isolates, which grew on sheep-blood agar incubated in room air at 35° C, appeared as gram-positive cocci in short chains or pairs and were catalase-negative. During the first 18 hours of incubation they were  $\alpha$ -hemolytic and were therefore identified as *viridans* streptococci. Further testing carried out by reference laboratories identified them as *S. iniae*. Strains from Cases 1, 2 and 3 were bacitracin-resistant; however, the strain from Case 4 was susceptible. Pulsed-field gel electrophoresis patterns of chromosomal *Sma*I digests of all four isolates were identical. Microbroth-dilution testing for susceptibility found all isolates to be susceptible to  $\beta$ -lactams, macrolides, trimethoprim-sulphamethoxazole, tetracycline, and the fluoroquinolones.

It is important to determine whether or not this is truly a new emerging pathogen or a previously unrecognized disease. It may have gone unrecognized for several reasons. Patients presenting with a wound infection of an extremity may not have skin wound or blood cultures performed. Further, the isolation of a *viridans* streptococci from a wound swab or blood may be dismissed as a contaminant and would likely not be further characterized. Even if

a *viridans* streptococci was further characterized in the laboratory by one of the currently available identification systems, *S. iniae* is not in current database systems and the possible connection with a fish-related injury may not be made.

There are, however, reasons to suspect that this is a new pathogen. It is unlikely that an infection resulting in such an acute clinical presentation with clear association to the preparation of fresh, whole fish would have gone unrecognized for any length of time. It is also likely to have been recognized as an occupational risk in aquaculture workers. In addition, it is a newly recognized pathogen in commercial fish farms that is able to spread quickly under conditions of intensive aquaculture, such as may occur with the increasing commercial success of tilapia farming.

The routine laboratory should readily be able to make a preliminary identification of *S. iniae* through several of its characteristics. In an atmosphere of 5% CO<sub>2</sub> at 24 hours it has a characteristic type of hemolysis consisting of a narrow zone of  $\beta$ -hemolysis next to the colony edge; a wider, diffuse zone of  $\alpha$ -hemolysis; and another outer narrow zone of  $\beta$ -hemolysis. *S. iniae* is  $\beta$ -hemolytic when grown in an anaerobic environment. *S. iniae* is non-groupable with Lancefield group A through U antisera. In addition, the pyrazinamidase and leucine aminopeptidase tests are positive, but the Voges-Proskauer test is negative and the organism may have variable susceptibility to bacitracin.

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## Editorial Comment

This report describes the first documented human infections with *S. iniae*, a pathogen that has caused central nervous system disease in aquacultured freshwater and marine fish. The identification of these first four cases prompted the formation of an investigative team of hospital and health unit staff from the Greater

Toronto Area (GTA), the Ontario Ministry of Health, the Department of Fisheries and Oceans, and LCDC. The team identified four areas requiring immediate study.

The first two areas of study involve case finding. Since three of the four patients presented with cellulitis, the team is examining the relationship between this clinical syndrome and patient contact with whole, raw freshwater fish. Ten Toronto area hospitals are searching their medical records retrospectively to identify patients with upper limb cellulitis admitted from 1 October 1995 to 31 March 1996. Patients are being interviewed using a standard questionnaire to determine the extent of contact, if any, with whole, raw fish in the 72 hours before illness. When such contact is reported, microbiologic swabs for *S. iniae* are also obtained from identified retail fish outlets. The second case-finding initiative

involves a prospective evaluation of any patients currently presenting with upper limb cellulitis to emergency rooms of the 10 hospitals. Parallel to these investigations, samples from live, aquacultured fish from GTA suppliers and wholesalers are being collected and tested for *S. iniae*. Finally, stored invasive isolates of *S. viridans* from Toronto hospitals are being re-examined to determine if they are possibly *S. iniae*.

All four studies are now underway and data are being gathered and analysed at LCDC. As of 1 July, there have been two additional cases of confirmed human infection with *S. iniae*, and the pathogen has been isolated from some of the samples of fish collected. No isolates of *S. viridans* have retested as *S. iniae*. These investigations should clarify whether this is a new or previously unrecognized infection.

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