

Clinical and Microbial Characteristics of Invasive *Streptococcus pyogenes* Disease in New Caledonia, a Region in Oceania with a High Incidence of Acute Rheumatic Fever[∇]

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Received 19 June 2009/Returned for modification 18 September 2009/Accepted 18 November 2009

New Caledonia is an archipelago in the South Pacific with a high prevalence of acute rheumatic fever and rheumatic heart disease. Conducted in 2006, this study aimed at characterizing clinical manifestations and microbial features of isolates obtained from invasive *Streptococcus pyogenes* disease. Clinical and demographic data were collected prospectively. Isolates were biotyped, T typed, *emm* sequenced, and tested for antibiotic susceptibility. Detection of the *speA*, *speB*, *speC*, and *ssa* genes was also carried out. The estimated annual incidence of invasive *S. pyogenes* disease in 2006 was high at 38 cases/100,000 inhabitants in New Caledonia. Invasive isolates were obtained from 90 patients with necrotizing fasciitis (41 cases), bacteremia with no identified focus (12 cases), myositis (10 cases), septic arthritis (9 cases), erysipelas (8 cases), postpartum infection (4 cases), myelitis and osteomyelitis (3 cases), severe pneumonia (2 cases), and endocarditis (1 case). The most frequent associated comorbidities were skin lesions (71%) and obesity (29%). Thirty-one different *emm* types were identified, and the following six accounted for 54% of the isolates: *emm15* (15.5%), *emm92* (12.2%), *emm106* (8.9%), *emm74* (6.7%), *emm89* (5.6%), and *emm109* (5.6%). The *speA*, *speC*, and *ssa* genes were expressed at different frequencies in the various *emm* types. The first epidemiological study of invasive *S. pyogenes* disease in New Caledonia highlights that *emm* type distribution is particular and should be taken into account in the development of an appropriate vaccine. These findings support the prevention of pyoderma and other cutaneous lesions in order to limit the development of both invasive disease and poststreptococcal sequelae in the South Pacific.

Streptococcus pyogenes is a major human pathogen causing both mild infections such as pharyngitis and impetigo and severe infections, including sepsis, necrotizing fasciitis (NF), and lethal streptococcal toxic shock syndrome (STSS). Non-suppurative sequelae such as acute rheumatic fever (ARF) and rheumatic heart disease (RHD) are associated with high morbidity and mortality rates, especially in developing countries (6, 9, 21). *emm* typing based on sequence analysis of the variable distal part of the gene that encodes the M protein, a major virulence factor, is the “gold standard” method used to characterize *S. pyogenes* isolates. Currently, there are more than 170 different group A *Streptococcus* (GAS) *emm* types (7, 12). Since the late 1980s, there has been an increase in the number of reports of invasive infections caused by *S. pyogenes* in Europe and the United States, with a significant preponderance of the *emm1* and *emm3* types (1, 14, 18, 20). A few studies have recently reported a different GAS type distribution in developing countries and in indigenous populations (3, 17, 22). Knowledge of the *emm* type distribution in a region may shed more light on the pathogenesis of GAS infections and is crucial for selecting appropriate vaccine candidates which would include multiple M protective epitopes. Currently, a 26-valent M

protein-based vaccine in the preclinical testing phase is being developed for populations with a high risk of ARF or RHD (16, 19).

We report the first epidemiological study of invasive *S. pyogenes* disease in New Caledonia, an archipelago in the South Pacific where rheumatic fever is endemic (www.dass.gouv.nc). Our objectives were to characterize the demographic, clinical, and microbiological features of invasive *S. pyogenes* disease in 2006 in New Caledonia to determine the *emm* type distribution of GAS strains in the population.

(This study was presented at the XVII Lancefield International Symposium on Streptococci and Streptococcal Diseases, Porto Heli, Greece, 2008.)

MATERIALS AND METHODS

Bacterial isolates and patients. All isolates of *S. pyogenes* obtained as pure cultures from infected body sites of patients at the largest hospital in Nouméa, a 285-bed tertiary-care hospital serving most of the New Caledonian population, were sent to the microbiology laboratory of the Pasteur Institute, New Caledonia, between January and December 2006. Only one isolate per patient was analyzed.

Standard patient demographics data, including age, sex, ethnicity, and date and site of isolate collection were recorded. Medical records were also examined prospectively to assess underlying diseases or conditions that might have predisposed patients to invasive disease: skin trauma, injection drug use, varicella infection, alcohol abuse, use of nonsteroidal antiinflammatory drugs (NSAIDs), diabetes, immunosuppressive therapy, malignancy, and HIV infection. The overall fatality rate was assessed 30 days after the date of specimen sampling.

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[∇] Published ahead of print on 2 December 2009.

Case definitions. Invasive cases were defined as infections associated with the isolation of *S. pyogenes* from a normally sterile site (blood, cerebrospinal fluid, or other normally sterile fluid/tissue, e.g., peritoneal, pleural, and joint) or as clinical presentation of NF, myositis, or erysipelas associated with monomorphic culture of *S. pyogenes* from the infected lesion. Cases of STSS were defined according to published criteria (24).

Identification of *S. pyogenes*. Identification was based on beta-hemolysis on Columbia sheep blood agar (Oxoid, Dardilly, France), Gram staining, a negative catalase test, a positive pyrrolidonyl arylamidase test (Oxoid), and agglutination with Lancefield group A antiserum (Slidex, Streptokit; bioMérieux, Marcy-l'Etoile, France).

Susceptibility testing. Antimicrobial susceptibility to penicillin G, amoxicillin, erythromycin, clindamycin, tetracycline, rifampin, streptomycin, kanamycin, gentamicin, and vancomycin was tested by the disk diffusion method on Mueller-Hinton agar with 5% sheep blood, incubated overnight at 37°C in air enriched with 5% CO₂ using commercial discs (Bio-Rad) according to the guidelines and interpretation criteria of the antibiogram committee of the French Society for Microbiology (www.sfm.asso.fr).

Typing and detection of toxin or superantigen genes. Biotypes were obtained on rapid ID 32 Strep strips (bioMérieux) as previously described (5). T serotypes were determined on trypsinated bacteria by slide agglutination with type-specific antisera (Sevapharma, Prague, Czech Republic) (11).

The *emm* gene was amplified and sequenced as described previously (2). *emm* type assignments were determined according to the protocol of the Centers for Disease Control and Prevention (Atlanta, GA) available at <http://www.cdc.gov/ncidod/biotech/strep/strepblast.htm> (7).

A multiplex PCR procedure was performed as previously described to detect the *speA*, *speB*, *speC*, and *ssa* genes (8, 13).

Data analysis. Incidence rates by ethnocultural group were calculated by using the 1996 census of the New Caledonian population (<http://www.insee.fr>). The estimate for the entire population was based on population data for 2004 re-evaluated with an increase of 1.9% per annum. With an estimated 239,642 inhabitants in 2006, this Pacific island group is a discrete epidemiological entity with a multicultural population including Melanesians (44% of the total population), Europeans (34%), Polynesians (12%, mainly Wallisian-Futunians and Tahitians), and others (10%, mainly Chinese and Indonesians). Statistical analyses were performed by using the Student *t* test to compare mean ages and the χ^2 test, odds ratios (ORs) with 95% confidence intervals (95% CIs), and the Fisher exact test (for small numbers) to compare the distribution of categorical data (STATA, version 8).

RESULTS

A total of 90 cases of invasive *S. pyogenes* disease were identified in 2006. Isolates were obtained from skin or soft-tissue samples ($n = 64$ cases), blood ($n = 13$), synovial fluid ($n = 9$), pleural fluid ($n = 2$), amniotic fluid ($n = 1$), and spinal fluid ($n = 1$).

Since all of the patients with severe *S. pyogenes* infections are usually transferred to the main hospital of the country, we estimated that the annual incidence of invasive *S. pyogenes* disease in 2006 was 38 cases/100,000 individuals. The incidence by age or by major ethnocultural group showed that three different groups had a higher risk of developing invasive *S. pyogenes* disease: children under the age of 5 years, adults above the age of 64 years, and Melanesians (Fig. 1 and Table 1). The incidence of *S. pyogenes*-positive blood culture was estimated to be 10.4 cases/100,000 inhabitants in New Caledonia in 2006. No seasonal or geographical differences in the occurrence of invasive *S. pyogenes* disease were observed. The median age of patients was 24 years (mean age, 31 ± 24 years; range, birth to 95 years), and the incidence of infection was higher among males (68% of the cases). We observed an overrepresentation of severe *S. pyogenes* disease in the indigenous Melanesian population (66 cases, 73%) and an underrepresentation among Europeans (13 cases, 14%) compared with the global distribution of ethnic groups in New Caledonia ($P \leq$

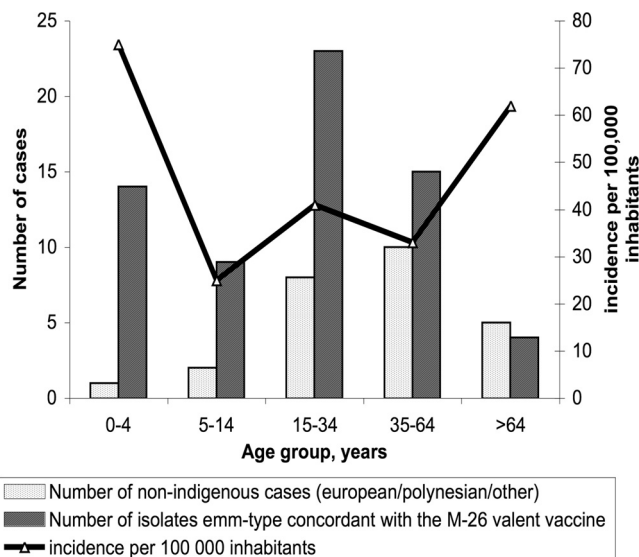


FIG. 1. Age distribution by ethnocultural group and incidence of invasive *S. pyogenes* disease in New Caledonia in 2006.

0.01). The proportions of patients with various underlying diseases, outcomes, and risk factors are shown in Tables 1 and 2. Skin and soft-tissue infections such as NF (41 cases), myositis (10 cases), erysipelas (8 cases), and bacteremia with no identified focus (12 cases) and arthritis (9 cases) were the most frequent clinical manifestations of invasive cases. Other clinical presentations included postpartum infections (four cases, including one case involving a mother and her baby), pleuropneumonia (two cases), osteomyelitis (two cases), myelitis, and endocarditis (one case of each). Puerperal fever cases were related to vaginal delivery in four women 21 to 32 years old. The three STSS cases, associated with one case of bacteremia and two cases of pneumonia, were fatal. Two-thirds of the patients underwent surgery, and 14% required intensive care. Irrespective of skin lesions, at least one comorbid disease was found in 52 (58%) of the 90 patients and was found significantly more frequently in adults up to 30 years old ($P \leq 0.01$) and in nonindigenous patients ($P \leq 0.03$). The most prevalent underlying conditions included obesity, cardiopulmonary diseases, ethanol abuse, and use of NSAIDs (55 [68%] of 81 studied). There were no cases of HIV infection or intravenous drug use. The presence of skin lesions in 71% of the patients was the predominant local predisposing factor for invasive infection, especially in patients without comorbidities ($P \leq 0.01$). They were wounds (40 cases), hematomas (15 cases), furuncles (5 cases), scabies lesions (4 cases), burns (2 cases), stings (2 cases), eczema (2 cases), purpura (2 cases), psoriasis (1 case), and varicella (1 case). NF was more frequent in children and young adults 5 to 29 years old ($P \leq 0.03$) and less frequent in Melanesians ($P \leq 0.01$). In a univariate analysis, *emm15* strains tended to be associated with the indigenous population, but this association was not statistically significant ($P \leq 0.06$).

Thirty-one different *emm* types were identified among the 90 isolates distributed as follows: *emm15* (14 cases), *emm92* (11 cases), *emm106* (8 cases), *emm74* (6 cases), *emm89* and *emm109* (5 cases each), *emm46* (4 cases), *emm49*, *emm65*,

TABLE 1. Clinical characteristics of 90 cases of invasive *S. pyogenes* disease in New Caledonia

Characteristic	No. of cases by major ethnocultural group		P value ^b	OR	95% CI	No. of cases by age group		P value ^b	OR	95% CI	No. of cases by sex		P value ^b	OR	95% CI
	Indigenous Melanesian (n = 66)	Nonindigenous European/Polynesian/other (n = 25)				≤30 yr (n = 54)	>30 yr (n = 37)				Male (n = 61)	Female (n = 30)			
Predominant clinical manifestations															
NF	24	17	≤0.01	0.3	0.1–0.9	29	12	≤0.05	NS	NS	31	10	NS		
Bacteremia	9	3	NS			5	7	NS			6	6	NS		
Myositis	9	1	NS			6	4	NS			7	3	NS		
Arthritis	6	3	NS			4	5	NS			8	1	NS		
Erysipelas	6	2	NS			1	7	≤0.01	0.1	0.1–0.7	4	4	NS		
Pneumonia	2	0	NS			0	2	NS			2	0	NS		
At least one comorbidity, except skin lesion ^a	33	19	≤0.03	0.3	0.1–0.9	21	31	≤0.01	0.1	0.1–0.4	32	20	NS		
Skin lesion	46	18	NS			37	27	NS			48	16	≤0.01	3.2	1.1–9.2
Molecular marker <i>emm15</i>	13	1	≤0.06	NS	NS	9	5	NS			7	7	NS		

^a Comorbidities studied: obesity, ethanol abuse, recent delivery, immunosuppression, dialysis, use of NSAIDs, cardiopulmonary disease, diabetes mellitus, recent (<7 days before) surgery, intravenous drug use, corticotherapy for >6 months, and malignancy treatment.

^b NS, not significant; significant, P > 0.05. The chi-square or Student t test was used, depending on the number of samples.

emm75, and *emm102* (3 cases each), *emm71* and *emm103* (2 cases each), *emm41*, *emm53*, *emm54*, *emm56*, *emm58*, *emm77*, *emm81*, *emm86*, *emm87*, *emm93*, *emm100*, *emm101*, *emm104*, *emm105*, and *emm123* (1 case each). One strain belonged to *st6735*; it was responsible for a postpartum infection and was isolated from the amniotic fluid of the mother, the throat of the baby, and the blood of both. An original strain belonged to a new sequence type, *st367* (available at <http://www.cdc.gov/ncidod/biotech/strep/strepblast.htm>), another belonged to *stG1750*, a sequence type previously identified from a group G streptococcal isolate, and *emm* gene amplification was unsuccessful for another strain. The proportions of diseases caused by the major *emm* types are shown in Table 3. Among the 62

typeable strains (68%), 13 different T types were observed and T3/13/B3264 was predominant (19 strains, 31%). The biotype distribution of strains was dominated by biotype 3 (52 [58%] of 90 cases), followed by biotypes 1 (18 cases), 29 (8 cases), 6 (5 cases), 5 (4 cases), 7 (2 cases), 8, and 13 (1 case each). There was a restricted association between certain *emm* types, T serotypes, biotypes, and resistance to tetracycline. The chromosomal *speB* gene was found in all isolates. The *speA*, *speC*, and *ssa* genes, which are associated with prophage elements, were present at different frequencies in various *emm* types, but the highest frequencies were found in the most prevalent types: *emm15* (*speA*, 93%; *speC*, 100%), *emm92* (*speC*, 91%), and *emm106* (*speC*, 100%). The analysis revealed that isolates of the same *emm* type shared a common or predominant toxin gene profile distribution. All of the strains were susceptible to all of the antibiotics tested but tetracycline. Tetracycline resistance, which was detected in nine strains (10%), was distributed among six different *emm* types, including *emm109* (three of the five isolates of this *emm* type were resistant), *emm65* (two cases), *emm53* (one case), *emm58* (one case), *emm104* (one case), and *stG1750* (one case).

DISCUSSION

This study constitutes a first approach regarding the burden caused by *S. pyogenes* disease in New Caledonia, which is a French overseas archipelago located in the South Pacific, about 2,000 km northeast of Sydney, Australia. The Department and Agency of Health and Social Affairs in New Caledonia (<http://www.dass.gouv.nc/>) annually updates the number of cases of ARF. In 2002, the incidence of ARF, which was estimated at 9.8 cases/100,000 inhabitants among the whole population of New Caledonia, reached 85.6 cases/100,000 children 5 to 19 years old, about 200 cases/100,000 Melanesians. This information is consistent with published data from neighboring countries where active surveillance is established; the median estimated incidence of ARF cases in children 5 to 14

TABLE 2. Clinical characteristics of invasive *S. pyogenes* disease in New Caledonia, 2006

Characteristic	No. (%) of isolates ^a
Comorbidities	
Skin lesion.....	64 (71)
Obesity.....	26 (29)
Cardiopulmonary disease.....	12 (13)
Ethanol abuse.....	10 (11)
Use of NSAIDs.....	7 (8)
Diabetes mellitus.....	6 (7)
Recent delivery.....	6 (7)
Dialysis.....	3 (3)
Malignancy.....	3 (3)
Corticotherapy for >6 month.....	2 (2)
Surgery <7 days before.....	2 (2)
Other ^b	4 (4)
Outcome	
Death.....	3 (3)
Surgical site drainage.....	57 (63)
Assisted ventilation.....	9 (10)
ICU admission.....	13 (14)

^a Total n = 90.

^b Other comorbidities studied: no intravenous drug use, one varicella infection, one case of immunosuppressive therapy, two malignancies, and no HIV infection.

TABLE 3. Correlation between predominant clinical manifestations and *emm* types of invasive *S. pyogenes* strains

Clinical manifestation(s) or parameter	Total no. of cases	No. with following <i>emm</i> type:						
		<i>emm</i> 15	<i>emm</i> 92	<i>emm</i> 106	<i>emm</i> 74	<i>emm</i> 89	<i>emm</i> 109	Other
NF	41	8	5	4	3	1	2	18
Bacteremia								
No identified focus	12	2	2	1	2	0	0	5
STSS ^a	1				1			
Myositis	10	1	1	1	0	2	1	4
Septic arthritis	9	0	1	0	0	2	1	5
Erysipelas	8	1	1	0	0	0	1	5
Postpartum infection ^b	4	0	1	0	1	0	0	2
Osteomyelitis	2	1	0	0	0	0	0	1
Pneumonia + STSS ^a	2	0	0	2	0	0	0	0
Endocarditis	1	0	0	0	0	0	0	1
Myelitis	1	1	0	0	0	0	0	0
Total (% of overall total)	90	14 (15.5)	11 (12.2)	8 (8.9)	6 (6.7)	5 (5.6)	5 (5.6)	41 (45.5)

^a Fatal.^b Four cases, including one mother-and-baby case due to an *st6735* strain.

years old has been estimated to reach 374 cases/100,000 inhabitants in the Pacific islands and indigenous populations of Australia and New Zealand versus 0.5 case/100,000 people in developed countries (6). In temperate regions, rheumatic fever is usually associated with throat infection but data suggest that *S. pyogenes* skin infections might play a greater role in the tropics (4, 15). Interestingly, in the present study conducted in New Caledonia, two cases of ARF were detected among the 90 patients with invasive GAS disease. Indeed, the original *S. pyogenes emm* type distribution observed among invasive *S. pyogenes* diseases might be related to the local environmental and host risk factors for infection, but it seems to contribute weakly to the high prevalence of ARF in New Caledonia, as previously described in indigenous children in New Zealand (6).

Our study confirmed that invasive *S. pyogenes* disease occurs at greater rates in New Caledonia than in Western countries and that these rates are similar to those reported for other countries in the Pacific, such as Fiji, and for the indigenous populations of Australia and New Zealand (6, 15, 17, 22, 23). Thus, the incidence of *S. pyogenes*-positive blood culture was five times higher in New Caledonia than in metropolitan France in 2006 (report of the French National Institute of Health Surveillance) but was similar to that in neighboring countries such as Fiji (22). Invasive GAS disease predominantly affected the elderly, over 64 years old, with coexisting medical conditions, as in most industrialized and developing countries (6). The high incidence among children in New Caledonia, at 75 cases/100,000 young children less than 5 years old, was similar to those reported in other developing countries and even twice as high as that in Fiji (22).

NF, other skin or soft-tissue infections, and bacteremias of cutaneous origin were more frequently reported in patients

less than 30 years old. Interestingly, indigenous Melanesian children (under 15 years old) are overrepresented (23 out of 26 cases, $P = 0.03$). The high proportion of young male Melanesians hospitalized for invasive *S. pyogenes* disease associated with skin lesions is in accordance with a previous study on the strong role of traditional behavior and environmental conditions in the development of impetigo in the tropics (4). In contrast, comorbidities, bacteremia, intensive care unit (ICU) admission, and being nonindigenous accounted for an increasing proportion of severe *S. pyogenes* cases as age increased. The low case fatality rate in our study (3.3%), compared to the rate of 32% reported in Fiji, remains unexplained (22).

The high genetic diversity of our *S. pyogenes* collection (31 different *emm* types were identified among 90 strains) confirms previous findings that *S. pyogenes* isolates from the tropics show considerable *emm* type variability. Furthermore, *emm*1, *emm*3, and *emm*4, the most prevalent types reported in the western world, were absent from our findings (14, 19). Moreover, the *emm* type distribution identified in this study was original and characterized by six predominant *emm* types (*emm*15, *emm*92, *emm*106, *emm*74, *emm*89, and *emm*109), accounting for 54% of the 90 strains. This distribution differed significantly from that in neighboring areas such as Hawaii, Fiji, and North Queensland, Australia (10, 22, 17). In contrast to these previous studies, in which no previous dominant *emm* type or clone has been demonstrated, we described the first predominance of the *emm*15 type among indigenous Melanesians. These *emm* type findings could be used to estimate the potential benefits of the proposed 26-valent M protein-based vaccine (which has successfully completed a phase 2 trial) for age groups at the highest risk of developing invasive *S. pyogenes* disease (children <5 years old and adults ≥65 years old) by checking whether vaccine types M1, -1.2, -2, -3, -5, -6, -11,

-12, -14, -18, -19, -22, -24, -28, -29, -33, -43, -59, -75, -76, -77, -89, -92, -94, -101, and -114 would be effective against the isolates reported in this study (16, 19). The number of children <5 years old diagnosed with invasive GAS disease due to the types represented by the 26-valent vaccine was 5 (33%) of 15 cases, and the number of adults ≥ 65 years old diagnosed was 2 (22%) out of 9. Despite the absence of pharyngitis *S. pyogenes* isolates in our study, the absence of known causative rheumatogenic strains in our *S. pyogenes* collection (M1, -3, -5, -6, -14, -18, -19, and -24) and the unusual distribution of *emm* types highlight the difficulties in building a universal M valence vaccine that is effective within our borders.

This is the first epidemiological study of invasive *S. pyogenes* disease in New Caledonia, a region with a high incidence of ARF. This study highlights an *emm* type distribution that is particular to New Caledonia and should be taken into account in the development of an appropriate vaccine. The reported incidence is far greater in indigenous communities than in other communities. Soft tissues were the most common sites of infection. These findings call for better prevention of pyoderma and other cutaneous lesions to limit the development of severe invasive disease. Further studies are ongoing to specify the role of the predominant *emm* types in ARF or other poststreptococcal sequelae in the South Pacific.

ACKNOWLEDGMENTS

We thank Gis lene Collobert and Fran oise Charavay for excellent technical assistance. We gratefully acknowledge Paul Martin for lending support to the development of molecular epidemiology in New Caledonia. We also thank all of the medical department of the Noum e Hospital for participating in this project.

We have no conflict of interest in relation to this work.

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