Health care-associated *Staphylococcus aureus* pneumonia

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INTRODUCTION: While *Staphylococcus aureus* is an uncommon but serious cause of traditional community-acquired pneumonia (CAP), it is a predominant cause of nosocomial pneumonia in addition to the unique clinical entity of health care-associated pneumonia (HCAP). A cohort of bacteremic *S aureus* pneumonia cases was reviewed to determine the role of HCAP among the cohort, and to assess for differences between CAP and HCAP.

PATIENTS AND METHODS: Bacteremic *S aureus* pneumonia cases were identified from a prospective study of all patients diagnosed with CAP who presented to hospitals in Edmonton, Alberta, between November 2000 and November 2002. These cases were subsequently reviewed retrospectively. Demographic, clinical and microbiological data were obtained, and patients were classified as having CAP or HCAP. Relatedness of isolates was determined by pulsed-field gel electrophoresis analysis in conjunction with epidemiological information.

RESULTS: There were 28 cases of bacteremic *S aureus* pneumonia identified. Fifty-seven per cent were reclassified as having HCAP, and 43% remained classified as having CAP. The CAP cohort was significantly younger than the HCAP cohort (mean age 49.0±23.7 years versus 67.8±18.6 years; P=0.035) with higher rates of intravenous drug use (50% versus 0%; P=0.002). Long-term care facility residence (44%) was common in the HCAP cohort. The HCAP cohort presented with more severe illness, having a higher mean pneumonia severity index score (143.1±41.1 versus 98.2±54.6; P=0.028), and despite fewer embolic complications, there was a trend toward a significantly higher mortality rate (31% versus 0%; P=0.052). Two community-acquired isolates cultured in the setting of intravenous drug use were methicillin-resistant, and no isolates were positive for Panton-Valentine leukocidin. There was evidence of relatedness involving 44% of the HCAP isolates by pulsed-field gel electrophoresis analysis.

CONCLUSION: HCAP accounts for a significant number of cases that, when using traditional definitions, would be classified as CAP. Severity of illness and mortality was excessive within the HCAP group. There was evidence of relatedness and spread of common strains in the HCAP cohort. The present study supports recommendations for treatment guidelines directed toward the entity of HCAP and the empirical coverage of *S aureus* among certain high-risk groups.

Key Words: *Community-acquired pneumonia; Health care-associated pneumonia;* Staphylococcus aureus

Les pneumonies à *staphylocoque doré* associées aux soins

INTRODUCTION : Le *staphylocoque doré* est une cause peu courante mais grave de pneumonie non nosocomiale (PNN) classique, mais c'est une cause prédominante de pneumonie nosocomiale en plus de l'entité clinique de pneumonie associée aux soins (PAS). On a évalué une cohorte de cas de pneumonie à *staphylocoque doré* bactériémique pour établir le rôle de la PAS au sein de la cohorte et pour évaluer les différences entre la PNN et la PAS.

PATIENTS ET MÉTHODOLOGIE : On a repéré les cas de pneumonie à *staphylocoque doré* bactériémique au moyen d'une étude prospective de tous les patients atteints d'une PNN diagnostiquée qui ont consulté dans les hôpitaux d'Edmonton, en Alberta, entre novembre 2000 et novembre 2002. Ces cas ont ensuite fait l'objet d'une analyse rétrospective. On a obtenu les données démographiques, cliniques et microbiologiques, et on a reclassé les patients entre une PNN et une PAS. On a déterminé le rapprochement des isolats au moyen d'une analyse d'électrophorèse en champ pulsé conjointement avec l'information épidémiologique.

RÉSULTATS : On a repéré 28 cas de pneumonie à *staphylocoque doré* bactériémique. Cinquante-sept pour cent ont été reclassés parmi les PAS, et 43 % parmi les PNN. La cohorte de PNN était considérablement plus jeune que celle de PAS (âge moyen de 49,0±23,7 ans par rapport à 67,8±18,6 ans; P=0,035) et s'associait à des taux plus élevés de médicamentation intraveineuse (50 % par rapport à 0 %; P=0,002). La cohorte de PAS habitait couramment (44 %) dans un établissement de soins de longue durée. Cette cohorte présentait une maladie plus grave et un indice moyen de gravité de la pneumonie plus élevé (143,1±41,1 par rapport à 98,2±54,6; P=0,028), et malgré le moins grand nombre de complications emboliques, on remarquait une tendance vers un taux de mortalité considérablement plus élevé (31 % par rapport à 0 %; P=0,052). Deux isolats non nosocomiaux cultivés pendant une médicamentation intraveineuse étaient méthicillinorésistants, et aucun isolat n'était positif à la leucocidine de Panton-Valentine. On a constaté un rapprochement touchant 44 % des isolats de PAS au moyen de l'analyse d'électrophorèse en champ pulsé.

CONCLUSION : La PAS représente un nombre important de cas qui, selon les définitions classiques, seraient classés parmi les PNN. La gravité de la maladie et la mortalité étaient excessives au sein du groupe de PAS. On a constaté un rapprochement et une propagation des souches courantes au sein de la cohorte de PAS. La présente étude étaye les recommandations de lignes directrices de traitement orientées vers l'entité de la PAS et la couverture empirique du *staphylocoque doré* au sein de certains groupes très vulnérables.

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Health care-associated pneumonia (HCAP) is being increasingly recognized as a clinical entity with significant morbidity and higher mortality than traditional community-acquired pneumonia (CAP) (1). With unique epidemiological, clinical and bacteriological characteristics, HCAP should be considered in the differential diagnosis of individuals with recent health care contact who present to hospitals with signs and symptoms of lower respiratory tract infection. Although presenting from the community, relevant health care contact is considered to include long-term care facility (LTCF) residence, ambulatory clinic hemodialysis, intravenous chemotherapy or home intravenous therapy, specialized home nursing care and recent hospitalization in an acute care hospital. When an individual presents with health care contact of this nature, empirical therapy may be tailored to the probable causative pathogens of HCAP, including *Staphylococcus aureus*. The American Thoracic Society and the Infectious Diseases Society of America have recently published guidelines that address the management of HCAP (2).

Although generally uncommon as a cause of CAP, *S aureus* has been implicated as a predominant pathogen in HCAP (1). *S aureus* pneumonia has classically been described as a secondary bacterial infection in the setting of primary influenza virus upper respiratory tract infection (3-8). However, *S aureus* has a long history as a cause of nosocomial pneumonia (9,10), and has been known for years to play a significant role in nursing home-acquired pneumonia (11). Thus, as health care expands further into the community with shorter inpatient stays and more expansive outpatient management, the predominance of HCAP, and thus *S aureus* pneumonia, can be expected to increase.

In the present observational study, a cohort of *S aureus* pneumonia cases presenting from the community were reviewed to determine the role of HCAP. Cases were identified from a larger prospective study of CAP cases in Edmonton, Alberta, over a two-year period and reviewed retrospectively. Cases were determined to be community acquired or health care associated. Epidemiological, clinical and microbiological data were analyzed.

PATIENTS AND METHODS

Patients older than 17 years of age who presented to hospitals in Edmonton, Alberta, between November 2000 and November 2002 were eligible for the study. Four teaching hospitals, two community hospitals and one freestanding emergency centre in Edmonton participated. Patients presenting with at least two of the following were managed according to a critical pathway for treatment of CAP: fever (body temperature higher than than 38°C), productive cough, chest pain, shortness of breath and crackles on auscultation, in addition to a chest radiograph interpreted as pneumonia (12). Pregnant or nursing women, neutropenic patients (white blood cell count less than 1.0×10^9/L), critical care patients, cystic fibrosis patients and patients hospitalized within 48 h before presentation were ineligible for the treatment pathway.

As per the critical pathway protocol, patients who were admitted to hospital had blood cultures drawn, and those who were treated for pneumonia on an ambulatory basis had blood cultures performed at the discretion of the attending physician. Data collected on all patients included demographic variables, signs and symptoms at presentation, comorbidities and predisposing factors, laboratory values, microbiology results and diagnostic imaging, as well as course of treatment and outcome. A pneumonia severity index (PSI) score was calculated using a validated prognostic scoring model (13). Given the low sensitivity and specificity of sputum cultures, the causative organism was determined to be the definite source of infection only when isolated from blood or pleural fluid (14). To provide a strict analysis of patients with *S aureus* pneumonia, only patients with blood cultures positive for *S aureus* were included in the study cohort and underwent further chart and radiological review.

Clinical analysis

All cases were initially considered to be community acquired based on traditional definitions. However, on further review, a case was reclassified as health care associated if one of the following criteria was fulfilled: the patient received home intravenous therapy or specialized home nursing care within the 30 days before the infection; attended a hospital or hemodialysis clinic, or received intravenous chemotherapy within the 30 days before the infection; was hospitalized in an acute care hospital for a minimum of two days in the 30 days before infection; or resided in an LTCF. To determine the appropriate classification, information gathered by research nurses at the time of entry into the study was reviewed, and cases were retrospectively reviewed by one of the authors (DW) using inpatient hospital charts in every case and outpatient clinic charts as available.

On retrospective review of each case, the pathogenesis of the bacteremic pneumonia was also assessed. If *S aureus* infection was determined to have originated in the respiratory tract, it was defined as a primary *S aureus* pneumonia. This designation was based on clinical signs and symptoms of respiratory tract infection preceding or coinciding with the isolation of *S aureus* from blood, with conditions predisposing to primary pulmonary infection and without a further extrapulmonary source that may have predisposed to hematogenous seeding of the lungs. Infection determined to have originated outside of the respiratory tract with subsequent seeding of the lungs was defined as a secondary *S aureus* pneumonia. This classification was based on clinical evidence of an extrapulmonary source of *S aureus* infection, such as endocarditis, that appeared to precede the development of pulmonary infection, or radiographic evidence, such as multiple nodular cavitary lesions, that was suggestive of hematogenous spread to the lungs.

Demographic and clinical data of the CAP and HCAP groups were compared. Statistical analysis of means was performed using the unpaired *t* test with Welch correction. Nominal data were analyzed using Fisher's exact test. A two-tailed P value was calculated, and $P<0.05$ was considered significant.

Microbiological analysis

S aureus isolates were identified by routine laboratory procedures. Susceptibility assays were performed using VITEK instrumentation (bioMerieux Inc, USA). VITEK cards (GPS-105) for susceptibility assays were inoculated and incubated according to the manufacturer's recommendations (bioMerieux Inc). Methicillin-resistant *S aureus* (MRSA) was determined as per the Clinical and Laboratory Standards Institute guidelines (15) using an oxacillin screen plate assay. Any isolates exhibiting growth on the screen plate were further characterized by detection of the penicillin-binding protein 2' (PBP2') using the PBP2' latex agglutination test (Oxoid Ltd, United Kingdom) according to the manufacturer's instructions. All *S aureus* isolates exhibiting growth on the oxacillin screen plate and that were PBP2'-positive were considered to be MRSA. All isolates were

TABLE 1
Demographics and severity of pneumonia among *Staphylococcus aureus* pneumonia study population

Demographics	Overall (n=28)	CAP (n=12)	HCAP (n=16)	P
Mean age ± SD, years	59.7±22.6	49.0±23.7	67.8±18.6	0.035
Age ≥65 years, n (%)	14 (50)	4 (33)	10 (62)	0.252
Male sex, n (%)	14 (50)	5 (42)	9 (56)	0.704
Current smoker, n (%)	10 (36)	8 (67)	2 (12)	0.005
COPD, n (%)	6 (21)	2 (17)	4 (25)	0.673
Congestive heart failure, n (%)	6 (21)	2 (17)	4 (25)	0.673
Hypertension, n (%)	8 (29)	3 (25)	5 (31)	1.000
Diabetes mellitus, n (%)	6 (21)	0 (0)	6 (38)	0.024
Active neoplasm, n (%)	2 (7)	0 (0)	2 (12)	0.492
HIV, n (%)	2 (7)	2 (17)	0 (0)	0.175
Hepatitis C, n (%)	7 (25)	5 (42)	2 (12)	0.103
Intravenous drug use, n (%)	6 (21)	6 (50)	0 (0)	0.002
Pneumonia severity risk class, n (%)				
I	2 (7)	2 (17)	0 (0)	0.175
II	2 (7)	2 (17)	0 (0)	0.175
III	3 (11)	1 (8)	2 (12)	1.000
IV	11 (39)	5 (42)	6 (38)	1.000
V	10 (36)	2 (17)	8 (50)	0.114
Mean PSI ± SD	123.8±51.6	98.2±54.6	143.1±41.1	0.028
Seasonal distribution, n (%)				
Winter	8 (29)	4 (33)	4 (25)	0.691
Spring	6 (21)	1 (8)	5 (31)	0.196
Summer	9 (32)	5 (42)	4 (25)	0.432
Autumn	5 (18)	2 (17)	3 (19)	1.000

CAP Community-acquired pneumonia; COPD Chronic obstructive pulmonary disease; HCAP Health care-associated pneumonia; PSI Pneumonia severity index

TABLE 2
Complications and outcomes among 28 patients with *Staphylococcus aureus* pneumonia

Complications and outcomes	Overall (n=28)	CAP (n=12)	HCAP (n=16)	P
Endocarditis, n (%)	9 (32)	6 (50)	3 (19)	0.114
On clinical diagnosis	4 (14)	2 (17)	2 (12)	1.000
On echocardiography	5 (18)	4 (33)	1 (6)	0.133
Cerebral emboli, n (%)	1 (4)	1 (8)	0 (0)	0.429
Epidural abscess, n (%)	2 (7)	2 (17)	0 (0)	0.175
Osteomyelitis, n (%)	5 (18)	3 (25)	2 (12)	0.624
Septic arthritis, n (%)	5 (18)	4 (33)	1 (6)	0.133
Mortality, n (%)	5 (18)	0 (0)	5 (31)	0.052
Mean LOS ± SD, days	24±18.9	31±21.2	19±15.8	0.126

CAP Community-acquired pneumonia; HCAP Health care-associated pneumonia; LOS Length of stay

tested for the presence of the Panton-Valentine leukocidin gene by polymerase chain reaction using primers established by Lina et al (16). A positive control was run concurrently with the test samples.

Molecular typing with pulsed-field gel electrophoresis (PFGE) was used to further characterize all the *S aureus* strains. The protocol was carried out as described by Mulvey et al (17). Analysis was performed using the Bio-Rad Gel Documentation System (Bio-Rad Laboratories, USA) and BioNumerics Software (Applied Maths, USA). A dendrogram was generated using the Dice coefficient with 1% tolerance. The molecular relatedness of strains was interpreted by PFGE analysis according to criteria described by Bannerman et al (18). Identical PFGE patterns were considered to be the same strain. Banding patterns with three or less band differences were considered to be subtypes. Banding patterns with more than three band differences were interpreted to be different strains. Epidemiological data were used to guide the interpretation of the molecular data.

RESULTS

Clinical analysis

Of 3043 patients who met the inclusion criteria for entry into the larger prospective CAP study between November 2000 and November 2002, 2008 patients (66%) had blood cultures performed, and 28 patients with bacteremic *S aureus* pneumonia were identified. Of these 28 patients, 23 were admitted on initial presentation, while five patients had blood cultures drawn in conjunction with initial ambulatory management. Twelve of the 28 patients (43%) remained classified as having CAP while 16 patients (57%) met criteria for HCAP.

The demographic features are presented in Table 1. Two distinct populations presented from the community with *S aureus* pneumonia. The CAP cohort was significantly younger than the HCAP cohort (mean age 49.0±23.7 years versus 67.8±18.6 years; P=0.035), with higher rates of smoking (67% versus 12%; P=0.005) and intravenous drug use (IVDU) (50% versus 0%; P=0.002). In contrast, the HCAP cohort was generally older, with higher rates of noninfectious chronic disease, such as diabetes mellitus (38% versus 0%; P=0.024). As expected with systemic *S aureus* infection, both cohorts tended to present with severe illness. Overall, 75% of the entire cohort presented with a risk class IV or V PSI score; however, the HCAP group presented with more severe illness overall and a significantly higher mean PSI score (143.1±41.1 versus 98.2±54.6; P=0.028)

There was no trend in seasonal distribution and none in the two cohorts were reported to have had a preceding influenza-like illness; none were tested for influenza. The most common presenting symptoms overall (data not shown) included dyspnea (79%), fever (64%) and cough (61%). Common laboratory findings included anemia (85% had a hemoglobin level lower than 135 g/L), neutrophilic leukocytosis (64% had a white blood cell count higher than 11.0×10^9/L, 78% had a neutrophil count higher than 7.5×10^9/L) and renal dysfunction (50% had a creatinine level higher than 130 µmol/L). Chest radiographs revealed effusion in 54% of individuals and cavitation in 18% of inidividuals.

Complications and outcomes are shown in Table 2, and distinct differences between the CAP and HCAP cohorts are again noted, although none reached statistical significance. Those with community-acquired *S aureus* pneumonia were noted to have higher rates of complications generally associated with *S aureus* bacteremia. Complications included endocarditis (50% versus 19%; P=0.114), cerebral emboli (8% versus 0%; P=0.429), epidural abscesses (17% versus 0%; P=0.175) and septic arthritis (33% versus 6%; P=0.133). However, despite fewer embolic complications, the HCAP cohort suffered a higher mortality rate (31% versus 0%; P=0.052), with a trend toward statistical significance in this latter category. A shorter mean

TABLE 3
Potential predisposing factors and pathogenesis among 28 patients with *Staphylococcus aureus* pneumonia

Predisposing factors and pathogenesis	n (%)
Health care-associated pneumonia (n=28)	16 (57)
Long-term care facility resident (n=16)	7 (44)
Acute care hospitalization within 30 days (n=16)	4 (25)
Skin portal (n=16)	8 (50)
Device-related (n=16)	3 (19)
Pacemaker (n=16)	2 (12)
Intravenous catheter (n=16)	1 (6)
Immunosuppression* (n=16)	5 (31)
Active neoplasm and chemotherapy (n=16)	2 (12)
Transplant (n=16)	1 (6)
Primary pneumonia and secondary bloodstream infection (n=16)	8 (50)
Primary bloodstream infection and secondary pneumonia (n=16)	8 (50)
Community-acquired pneumonia (n=28)	12 (43)
Intravenous drug use (n=12)	6 (50)
Skin portal (n=12)	9 (75)
Primary pneumonia and secondary bloodstream infection (n=12)	1 (8)
Primary bloodstream infection and secondary pneumonia (n=12)	11 (92)

**Immunosuppression is defined as hypogammaglobulinemia, CD4 lymphocyte count less than 200×10⁶/L, treatment with conventional immunosuppressives and corticosteroid use of oral prednisone ≥10 mg daily*

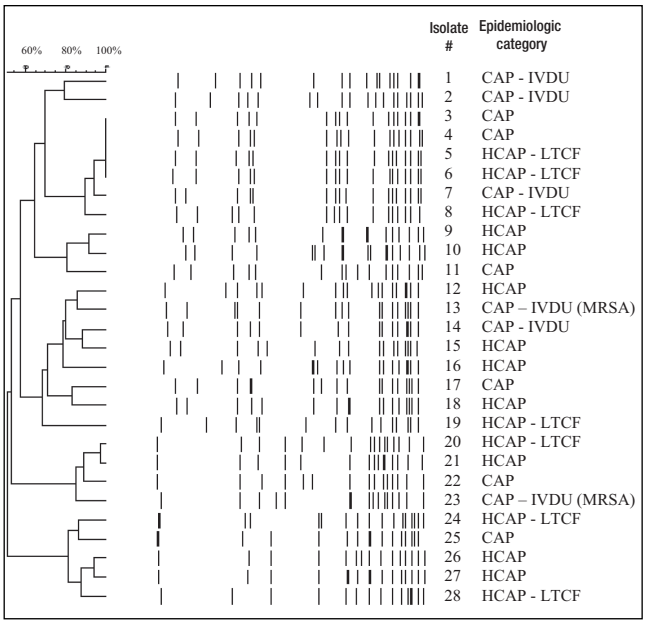

Figure 1) *Pulsed-field gel electrophoresis dendrogram analysis of* Staphylococcus aureus *isolates. CAP Community-acquired pneumonia; HCAP Health care-associated pneumonia; IVDU Intravenous drug use; LTCF Long-term care facility; MRSA Methicillin-resistant* S aureus

length of stay among the HCAP cohort was due, in part, to this higher mortality rate, because death occurred within 48 h of admission in two HCAP patients.

An assessment of the pathogenesis and summary of predisposing factors is provided in Table 3. In 11 of 12 cases (92%) of *S aureus* CAP, the pneumonia was determined to be secondary to hematogenous seeding of the lung parenchyma in the setting of a primary bacteremia. A break in skin integrity was the most common source of the primary bacteremia, with IVDU being the most frequent cause of the skin portal. A primary bloodstream infection with a secondary pneumonia was also common, although less so, among the HCAP cohort; this was observed in eight of 16 cases (50%). A break in skin integrity – frequently due to *S aureus* culture-positive decubitus ulcers, skin abrasions or infected intravascular catheters – was also the common source of the bacteremia among the HCAP cohort. LTCF residence was a prominent potential predisposing factor among the HCAP cohort, observed in seven of 16 (44%) cases. Readmission within 30 days of an acute care hospitalization was observed in four cases of HCAP (25%), although no single hospital predominated, because all four cases had been previously admitted to four different Edmonton hospitals.

Microbiological analysis

Susceptibilities were performed on 27 of 28 *S aureus* isolates because one of the isolates – isolate 12 shown in Figure 1 – failed to grow on the VITEK. Of the 27 isolates for which results were available, all were susceptible to vancomycin and rifampin. Eighty-five per cent of the isolates were beta-lactamase positive and, thus, penicillin resistant. One isolate was resistant to trimethoprim-sulfamethoxazole. Two isolates were found to be methicillin resistant, one of which was also resistant to clindamycin. Of these two MRSA isolates, both were cultured from individuals with a history of IVDU.

Polymerase chain reaction revealed that all isolates were negative for the Panton-Valentine leukocidin gene. The PFGE patterns of the 28 study isolates are illustrated in Figure 1. Three isolates, numbers 4, 5 and 6, were interpreted as having indistinguishable band patterns. Dendrogram analysis with epidemiological information showed that identical isolates 5 and 6 along with subtype 8 were recovered from three elderly residents of three different LTCFs in Edmonton in 2002. The LTCFs were located in separate areas of the city, and no further epidemiological link was clearly identified in these cases. Isolate 4 was cultured from an individual living in the community and was classified as a CAP isolate. Isolates 3 and 7 were also subtypes within this group. Both were classified as CAP isolates, with the latter cultured in the setting of IVDU.

Isolates 20 and 21 were subtypes by PFGE pattern and were cultured in the setting of health care-associated infections less than one month apart in 2001. Both individuals were elderly with multiple comorbidities and were admitted to the same acute care hospital. Isolate 20 was cultured from the blood of an 89-year-old woman who was an LTCF resident with a left base infiltrate and endocarditis involving a porcine mitral valve. Isolate 21 was cultured from a 66-year-old man with Hodgkin's lymphoma and bilateral patchy infiltrates. He was a palliative patient and died within hours of his admission.

Isolates 26 and 27 were also subtypes cultured from individuals with health care-associated infections. These isolates were both cultured in 2002. The former isolate was cultured from the blood and sputum of a 71-year-old man with metastatic small cell lung cancer and recurrent admissions for pneumonia. The latter strain was cultured from the blood of a 59-year-old quadriplegic man with chronic pressure ulcers and a left upper lobe infiltrate.

The two MRSA isolates were numbers 13 and 23. Both were CAP isolates cultured in the setting of IVDU; however, PFGE analysis demonstrated no relatedness. Further assessment

of the band patterns of these two isolates confirmed that the strains did not fall within a Canadian MRSA clonal prototype, or within the USA300 or USA400 prototypes.

DISCUSSION

In terms of epidemiology and pathogenesis, the clinical entity of *S aureus* pneumonia has evolved over time. A literature review, shown in Table 4, suggests some trends. Although a very heterogenous set of studies, the review suggested that the role of influenza has decreased in proportion to other risk factors over the past century, and has cycled in and out of the equation. Influenza remains an important predisposing factor; however, the contribution of other factors has grown. Table 4 shows the emergence of IVDU as an important risk factor for secondary *S aureus* pneumonia as highlighted by Julander et al (19), and MRSA as a major threat was prominent in a number of studies (20-22). *S aureus* pneumonia, as a significant nosocomial entity, is noted in Rebhan and Edwards' (23) 1960 review of 329 cases of staphylococcal pneumonia at The Hospital for Sick Children (Toronto, Ontario). In this 1950s cohort, 32% of the cases involved recent hospital contact and 3% of all cases occured in hospitalized premature infants.

With the significant role of the health care system and its extension into the community, *S aureus* has become a more frequent pathogen among cases of pneumonia presenting from the community. The American Thoracic Society and the Infectious Diseases Society of America have acknowledged HCAP as a unique and important clinical entity, with recognition of *S aureus* as a common causal pathogen (2). This designation is supported by our present study, which also found a significant number of *S aureus* pneumonia cases within a traditional CAP cohort that were found to be more precisely defined as HCAP.

This new designation also finds support in a recently published retrospective cohort study (1), which analyzed a large multi-institutional database of American acute care hospitals. In the study, Kollef et al (1) hypothesized that HCAP would involve pathogens more commonly associated with nosocomial pneumonia. This large study included 2221 patients with CAP, 988 patients with HCAP, 835 patients with hospital-acquired pneumonia and 499 patients with ventilator-associated pneumonia. The distribution of pathogens was somewhat unusual, in that *S aureus* was the most common pathogen in all four groups. It was noted in the related editorial that this may have been an artifact of the inclusion criteria (24). Nonetheless, the frequency of occurrence of *S aureus* in the HCAP group (46.7%) was comparable with the hospital-acquired pneumonia (47.1%) and the ventilator-associated pneumonia (42.5%) groups, and was significantly higher than the CAP group (25.5%).

Other investigators have also noted the relevance of distinguishing health care-associated infection from community-acquired infection. In a study of 504 bloodstream infections in North Carolina, USA, Friedman et al (25) found that 37% of bacteremic episodes that would normally have been classified as community-acquired, were more accurately identified as health care-associated. Similar to nosocomial infections, *S aureus* was prominent and in fact the most common pathogen.

A significant predisposing factor among the small cohort in our present study was the acquisition of health care in the community setting. Among the cohort, it was found that HCAP was more common than CAP, with the former identified in 16 cases (57%) and the latter in 12 cases (43%). While one-half of the CAPs occurred in the setting of active IVDU, the most prominent predisposing factor in the older and sicker HCAP group was a break in skin integrity providing a portal of entry for bacteremia, which occured in 50% of cases; LTCF residence was a factor in 44% of cases. All five patients who died were from the HCAP group and three of the five were LTCF residents. Although the number of cases was small, a distinction in terms of predisposing factors, and perhaps outcomes, appeared to emerge, demonstrating the importance of distinguishing between these differing cohorts.

With epidemiological data to guide the interpretation of PFGE analysis, we were able to examine the relatedness of *S aureus* isolates in the present study. Within the community setting of the study, three identical isolates with related subtypes and two further subtype pairs were identified from the 28 isolates. Among these, seven were HCAP isolates. There is evidence of relatedness among 44% of the HCAP isolates and, therefore, modest evidence to suggest the spread of common strains.

Furthermore, additional evidence of relatedness may be observed through the application of the less stringent Tenover et al (26) rules. Although isolates 9 and 10 did not meet the predefined study criteria as subtypes, by the Tenover et al rules, they would be classified as 'possibly related' based on a four- to six-band difference, consistent with two genetic events. These isolates were cultured one month apart in 2001. Both involved individuals with chronic disease closely linked to the health care system. Isolate 9 was isolated from a 41-year-old woman with primary pulmonary hypertension, who developed bacteremic *S aureus* pneumonia in the setting of an infected intravascular Broviac catheter. Isolate 10 was cultured from a 45-year-old splenectomized man with hepatitis C and alcohol-related cirrhosis, who had been undergoing routine paracenteses when he developed a large left lower lobe pneumonia and *S aureus* bacteremia. Both had been receiving regular outpatient care at medical clinics within the same hospital.

The present study also provides some insight into the demographics of *S aureus* HCAP and is relevant in light of recently published guidelines for the management of HCAP (2). These guidelines recommend that HCAP be empirically treated as a multidrug-resistant infection with knowledge of local resistance patterns with further guidance by the principles of antibiotic stewardship and the targeting of modifiable risk factors. In our small study, MRSA accounted for 7% of cases. The need for empirical MRSA coverage with vancomycin, linezolid or an alternative may be best determined at a local level with periodic review.

However, given the exclusion criteria of the study, the findings may not be applicable to all populations, specifically pregnant women, critical care patients, individuals with cystic fibrosis or neutropenia, and those recently hospitalized. Prior studies and knowledge of these groups may provide some insight into the epidemiology of pneumonia in these specific settings. For example, observational studies of pneumonia in pregnancy with routine microbiological investigations have suggested that the range of causal pathogens is similar to those of the nonpregnant adult (27). It may be assumed that should a pregnant woman have exposures that would put her at risk for health care-associated infection, she would also be at increased risk for *S aureus* pneumonia. Although, admittedly, clear evidence from focused studies is lacking.

In terms of the critically ill, studies have found that *S aureus* is a more prominent etiological agent in the setting of severe

TABLE 4
Literature review of *Staphylococcus aureus* pneumonia

Reference, year	n	BC+ (%)	Resp+ (%)	1° versus 2° (%)	BE (%)	Skin portal (%)	Influenza (%)	Mortality (%)	Location (years of study)	Comments
Current study	28	100	–	32/68	32	61	0	18	Edmonton, Alberta (2001–2002)	HCAP in 57% and CAP in 43%
Gonzalez et al (29), 2003	134	100	–	37/63	–	60	0	37	Madrid, Spain (1990–1995)	65 (48.2%) CAP patients with 47 (72.3%) 2° IVDU
Skull et al (30), 1999	13	100	–	23/77	0	'Most'	15	46	Darwin, Australia (1996–1997)	12 of 13 cases (92%) were community acquired
Gonzalez et al (20), 1999	54	100	–	–	–	88	–	41	Madrid, Spain (1990–1995)	All were MSSA, 63% had CVC and 70.4% were nosocomial
Gonzalez et al (20), 1999	32	100	–	–	–	63	–	56	Madrid, Spain (1990–1995)	All were MRSA, 88% had CVC and 93.8% were nosocomial
Tumbarello et al (31), 1996	19	53	79*	47/53	0	84	–	16	Rome, Italy (1986–1994)	All were HIV-positive patients, 84% had IVDUs, 68% had CAP
Musher et al (32), 1994	19	37	100*	74/26	26	26	–	32	Texas, USA (1989–1992)	Among 162 *S aureus* infections; 37% had CAP
Tsao et al (33), 1992	34	100	21†	21/79	12	32	–	–	Taipei, Taiwan (1985–1986)	Among 138 *S aureus* BSI cases; 62% had CAP
Kaye et al (34), 1990	31	32	74‡	100/0	0	0	–	32	New England, USA (1983–1988)	81% nosocomial, 13% CAP and 6% LTCF cases
Levine et al (35), 1990	8	38	100*	–	–	50	0	38	New York, USA (1986–1987)	HIV-positive cohort; seven of eight cases defined as CAP
Cafferkey et al (21), 1988	11	–	100*	64/36	–	36	–	18	Dublin, Ireland (1985–1987)	Nosocomial MRSA infection cohort
Watanakunakorn (36), 1987	44	100	100*	100/0	–	0	–	84	Ohio, USA (1980–1984)	66% nosocomial, 23% CAP and 11% LTCF cases
Woodhead et al (8), 1987	61	16	100§	–	1.6	–	25	30	Trent, England (1974–1984)	All cases defined as community-acquired
Lentino et al (22), 1985	12	33	100*	–	–	17	0	58	Ilinois, USA (1982–1983)	MSSA cohort , five nosocomial cases
Lentino et al (22), 1985	17	53	100*	–	–	65	6	82	Illinois, USA (1982–1983)	MRSA cohort, 16 nosocomial cases
Julander et al (19), 1983	13	100	–	0/100	92	100	–	–	Stockholm, Sweden (1977–1981)	BC+/PE/IVDU, prospective echo
Julander et al (19), 1983	16	100	–	0/100	75	100	–	–	Stockholm, Sweden (1965–1981)	BC+/PE/IVDU, retrospective echo
Naraqi and McDonnell (37), 1981	12	100	25*	16/83	8	83	0	25	Papua, New Guinea (1977–1979)	10 had SSTI; nine of 10 were community acquired
Musher and McKenzie (38), 1977	20	60	80*	55/45	45	–	–	15	Texas, USA (1971–1976)	Among 123 cases of *S aureus* infection
Rebhan and Edwards (23), 1960	329	2	100¶	–	–	17	0	14	Toronto, Ontario (1950–1958)	32% with recent hospital contact
Ede et al (4), 1959	36	6	100**	94/6	–	3	50	3	Illinois Naval Hospital, USA (1956–1958)	Includes the influenza epidemic of 1957–58
Robertson et al (7), 1958	38	–	100*	–	–	–	'Most'	47	Sheffield, England (1957)	During the influenza epidemic of 1957–58
Fisher et al (39), 1958	21	48	81††	67/33	–	14	0	67	Maryland, USA (1942–1956)	Six nosocomial cases with 100% mortality
Hausmann and Karlish (40), 1956	18	–	100*	–	–	–	6	0	Reading, England (1952–1954)	17 community and one nosocomial case
Finland et al (5), 1942	66	17	100††	100/0	–	–	100	32	Massachusetts, USA (1940–1941)	During the influenza epidemic of 1940–1941
Reimann (6), 1933	6	0	100‡‡	100/0	–	0	33	33	Minnesota, USA (1931–1933)	Four CAP and two nosocomial cases
Chickering and Park (3), 1919	155	1	100‡‡	100/0	–	–	100	99	South Carolina, USA (1918)	During the influenza epidemic of 1918

**Sputum cultures; †Bronchial brushing, secretion or sputum cultures; ‡Tracheal aspirate, direct lung aspirate, open lung biopsy, pleural fluid or bronchial brushing cultures; §Sputum, pleural fluid, tracheal aspirate or postmortem lung cultures; ¶Auger suction, bronchoscopic suction or pleural fluid cultures; **Throat, sputum or pleural fluid cultures; ††Sputum, pleural fluid or postmortem lung cultures; ‡‡Sputum or postmortem lung cultures. BC+ Blood culture-positive; BE Bacterial endocarditis; BSI Bloodstream infection; CAP Community-acquired pneumonia; CVC Central venous catheter; IVDU Intravenous drug use; LTCF Long-term care facility resident; MRSA Methicillin-resistant* S aureus*; MSSA Methicillin-sensitive* S aureus*; PE Pulmonary embolism; Resp+ Respiratory specimen culture-positive; SSTI Skin and soft tissue infection*

CAP requiring admission to an intensive care unit compared with less severe CAP requiring hospitalization or ambulatory management (14). *S aureus* may also be more prominent as a cause of pneumonia presenting from the community among the other groups excluded from the study. Certainly, the airways of cystic fibrosis patients are commonly colonized by *S aureus* within the first few years of life, and these individuals are prone to developing respiratory tract infection due to this pathogen at rates higher than the general population (28). The risk factors for the neutropenic group excluded from the study depend on the cause and duration of the neutropenia, although in general, this would certainly be a group predisposed to receiving frequent and specialized medical care. In this respect, selected cases would also be at increased risk for *S aureus* infection, although, akin to the cystic fibrosis patients, there would frequently be other opportunistic pathogens that need to be considered. Finally, patients hospitalized within 48 h of presentation were excluded from the current study, because the cohort was derived from a larger prospective CAP study. However, these cases would meet the definition of HCAP, and would be considered to be at risk for developing *S aureus* infections, including pneumonia.

With regard to the role of influenza, which has been classically described as a risk factor for the development of *S aureus* pneumonia, it is difficult to comment on the role that this predisposing viral infection may have played in the present study. It was noted that there was no trend in seasonal distribution, and none in the cohorts were reported to have had a preceding influenza-like illness. Furthermore, preceding influenza infection was unlikely to have contributed to the development of *S aureus* pneumonia in the present study, because influenza A was not prominent in the region over the two-year study period, with only 314 confirmed cases in the Capital Health region (Edmonton, Alberta), which consists of over one million people. Yet, none of the cohort were tested for influenza, and thus, the role of this viral pathogen as a predisposing factor cannot be absolutely delineated in the present study. Note also that influenza would predispose a patient to a primary *S aureus* pneumonia rather than a secondary pneumonia via hematogenous spread. Primary pneumonia accounted for only a fraction of the total cases in the study.

CONCLUSION

In the present series of 28 cases of bacteremic *S aureus* pneumonia presenting to hospital from the community, health care-associated infection accounted for the majority of cases that, using traditional definitions, would have been classified as CAP. The HCAP cohort was significantly older, presented with a higher mean PSI score and showed a trend toward a higher mortality rate. LTCF residence and skin portals including decubitus ulcers and intravascular lines were important predisposing factors for the development of *S aureus* HCAP. The cohort with community-acquired infection was younger in age, and had higher rates of smoking and IVDU.

MRSA accounted for a small but significant percentage of these *S aureus* HCAP cases. There is evidence of relatedness among 44% of the HCAP isolates in the present study and modest evidence to suggest spread of common strains. *S aureus* is a predominant HCAP pathogen, and the present study supports distinguishing between HCAP and CAP, as well as the empirical coverage of *S aureus* among certain high-risk groups.

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