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# Risk of community-acquired pneumonia requiring hospitalization in patients with spondyloarthritis

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***Abstract***

**Aims:** To compare the risk of community-acquired pneumonia (CAP) requiring hospitalization in spondyloarthritis (SpA) and non-specific back pain (NSBP), and to identify the risk factors for CAP in SpA.

**Methods:** A total of 2984 patients with SpA from 11 rheumatology centers and 2526 patients with NSBP from orthopedic units were reviewed from the centralized electronic database in Hong Kong. Incidence of CAP requiring hospitalization and demographic data including age, gender, smoking and drinking status, use of sulfasalazine, individual biological-disease modifying anti-rheumatic drugs (DMARDs) used, micro-organisms, other immunosuppressants or immunosuppressive states, use of steroid for more than ½ year, and co-morbidities were identified. Risks of CAP in SpA were compared with those in NSBP using propensity score regression method. Multivariate Cox regression model was used to identify the risk factors in SpA.

**Results:** CAP requiring hospitalization was found in 183 patients with SpA and 138 patients with NSBP. Increased risk for CAP was found in the following groups with SpA: all subgroups (hazard ratio (HR) 2.14, $p < 0.001$), without use of DMARDs (HR 2.64, $p < 0.001$), without psoriasis and not taking DMARDs (HR 2.38, $p < 0.001$). Infliximab (HR2.55, $p = 0.04$), smoking (HR 1.68, $p = 0.003$), comorbid psoriasis (HR 1.67, $p = 0.003$), and use of steroid for more than ½ year (HR 1.94, $p = 0.003$) were found to associate with CAP after adjustments for traditional risk factors.

**Conclusion:** Risk of CAP is increased in patients with SpA. Our data favor universal influenza and pneumococcal vaccination programs in the population. Rheumatologists should also advise smoking cessation and avoid long term steroid therapy.

***Keywords:*** biologics, community-acquired pneumonia, smoking, Spondyloarthritis, steroid, sulfasalazine, vaccination

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## Introduction

Spondyloarthritis (SpA) is a spectrum of diseases characterized by axial and peripheral joint inflammation with extra-articular features. It encompasses a number of rheumatological conditions including ankylosing spondylitis (AS), psoriatic arthritis (PsA), inflammatory bowel disease (IBD) associated SpA, reactive arthritis (ReA), undifferentiated SpA (uSpA), and human leucocyte antigen B27 (HLA-B27) associated uveitis.

Treatment of SpA has evolved significantly in the past decade. On one hand the development of biological agents makes remission an achievable goal, on the other hand risk of infection can be increased with these new therapies.[1] Community-acquired



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pneumonia (CAP) is one of the most important preventable infections. It has been reported as the leading infectious cause and the overall fifth-leading cause of mortality in the Global Burden of Disease Study.[2] Lower respiratory tract infections caused more than 2.6 million deaths worldwide in 2013,[3] with no global efforts spared in its prevention and reduction of disease burden.

Despite the high prevalence of CAP, epidemiological data in patients with SpA is sparse. The data could be important in guiding appropriate vaccination policy, including pneumococcal and influenzae vaccines. Previous randomized controlled trials (RCTs) have shown a low risk of serious infections in patients with AS with or without the use of anti-tumor necrosis factor (anti-TNF).[4] However, they may have been biased by an inclination towards highly selective populations and short durations of follow-up. From a centralized electronic database in Hong Kong, manually identified patients with SpA were compared with patients with non-specific back pain (NSBP) to assess the risk of CAP and its risk factors.

## Methods

This is a retrospective analysis of data from the Hospital Authority Clinical Management System (CMS), a centralized electronic database. Established in 1995, it contains complete medical records of all public hospitals in Hong Kong. The author (HYC) identified patients with expert diagnoses of SpA, AS, SpA with psoriasis, IBD-associated SpA, ReA, uSpA, and HLA-B27 associated uveitis by manually searching all electronic medical records of patients in 11 rheumatology centers (Queen Mary Hospital, Grantham Hospital, Tung Wah Hospital, Caritas Medical Centre, Pamela Youde Nethersole Eastern Hospital, Tseung Kwan O Hospital, Queen Elizabeth Hospital, Kwong Wah Hospital, Alice Ho Miu Ling Nethersole Hospital, Pok Oi Hospital, and Prince of Wales Hospital). We also included all patients with NSBP currently in the orthopedic units of a public hospital (Queen Mary Hospital) as controls. NSBP was defined as back pain without a specific and identified pathology such as trauma, tumor, infection, deformity, and nerve compression. First episode of CAP requiring hospitalization was recorded. Severe CAP was defined as pneumonia resulting in intensive care unit admission or death. Data were collected from December 1995 to June 2019 and were rechecked by another author (SCWC). Patients with rheumatological diseases in the control group were excluded from analyses.

Clinical data were retrieved. These included age, ethnicity, gender, dates of first and last follow-up, smoking and drinking status (defined as excessive alcohol use), date of CAP requiring hospitalization, severe CAP, history of psoriasis, history of IBD, subtypes of SpA, and comorbidities [diabetes mellitus (DM), stages of chronic kidney disease, malignancy, chronic lung disease, chronic heart disease, immune-suppressed state, and cerebrovascular accident], steroid use for more than ½ year. Chronic renal impairment was defined as chronic kidney disease stage 3 or above.[5] Chronic lung disease included asthma, chronic obstructive airway disease, bronchiectasis, and interstitial lung disease. Chronic heart disease included ischemic heart disease, congenital heart disease, heart failure, valvular heart disease, septal defect, and arrhythmia. Immune-suppressed state included congenital immunodeficiency, human immunodeficiency virus infection, other acquired immunodeficiency, and received chemotherapies. Cerebrovascular accident included both ischemic and hemorrhagic stroke. We also collected detailed drug histories including dates of initial use, and discontinuation of the following conventional disease modifying anti-rheumatic drugs (c-DMARDs) and biological disease modifying anti-rheumatic drugs (b-DMARDs): sulfasalazine, etanercept, infliximab, adalimumab, golimumab, certolizumab, and secukinumab. Immunosuppressants other than the above mentioned DMARDs were grouped together with immune-suppressed state as a single entity labeled as other immunosuppressants or immunosuppressive states. Micro-organisms identified in respiratory specimens were also recorded.

The clinical outcome assessed was the first episode of CAP requiring hospital admission. CAP was defined by fulfillment of all the following criteria: (1) admission with symptoms of pneumonia which included cough, sputum, shortness of breath, with or without fever; (2) chest X-ray or computed tomography showing consolidation, airspace opacity, or interstitial opacities, with or without pleural effusion as reported by an internist or a radiologist; (3) expert diagnosed pneumonia.

### *Duration of follow-up*

Duration of follow-up was defined as the time between first assessment at the rheumatology clinic or orthopedic clinic and one of the following endpoints: first admission due to CAP, death, or end of study.

### *Duration of DMARD use*

Duration of DMARD use was defined as the time between initial use of the DMARD, and one of the following endpoints: first admission due to CAP, discontinuation of the DMARD, death, or end of study.

### *Eligibility for free influenza, pneumococcal, and* Haemophilus influenzae *vaccines*

In Hong Kong, seasonal influenza vaccines have been provided free of charge to persons aged 50 years or above since 2006 and pneumococcal vaccines to those aged 65 or above since 2009. The government also provide free seasonal influenza vaccines to those immunocompromised (primary or secondary); have history of invasive pneumococcal disease, cerebrospinal fluid leakage or cochlear implant; have chronic cardiovascular, lung, liver, kidney diseases, DM or obesity; and those with chronic neurological conditions that can compromise respiratory functions or the handling of respiratory secretions. Eligibility criteria for these vaccines are reported in the results. All children younger than 5 years are vaccinated with *H. influenzae* serotype b (Hib) in Hong Kong.

### *Statistical analyses*

Crude incidence rates were described as the number of first episode CAP requiring hospitalization per 1000 patient-years of SpA and NSBP. Baseline characteristics of the two populations were described using Student's *t*-test and Pearson's chi-square test. Student *t*-test was used to compare between two continuous variables. Pearson's chi-square test was used to compare between two categorical variables.

Risks of CAP requiring hospitalization and severe CAP in patients with SpA and NSBP were compared using propensity score stratification method.[6,7] Known or potential risk factors for CAP were included in logistic regression to calculate the propensity score. The risk factors included age,[8–10] Chinese ethnicity, male gender,[11] smoking status,[9] drinking status,[11] history of psoriasis, history of IBD, use of sulfasalazine, etanercept, infliximab, adalimumab, golimumab, certolizumab, secukinumab, use of steroids for more than ½ year, diabetes,[12] chronic renal impairment,[12] malignancy,[13,14] chronic lung disease,[15] chronic heart disease,[12] other immunosuppressants or immunesuppressed states,[11] and cerebrovascular accident.[12] The score was grouped into pentiles with non-overlapping parts trimmed. Cox proportional hazard model (Cox regression model) stratified according the propensity score was used to determine the risk of CAP requiring hospitalization and severe CAP in patients with SpA with reference to NSBP. Duration of follow-up was used as the time variable. The method was repeated to compare the risk of CAP requiring hospitalization and severe CAP between patients with SpA and NSBP with the following subgroups: (i) patients without use of DMARDs, (ii) patients without psoriasis and not taking DMARDs. Results were expressed as hazard ratio (HR).

The mentioned risk factors for CAP requiring hospitalization and severe CAP in patients with SpA were screened out using univariate Cox regression analyses. Duration of individual DMARDs' use was included in the time variable. Since secukinumab is contra-indicated in IBD patients, they were excluded in the analysis of secukinumab. Significant independent variables with a $p$ value $< 0.10$ were included in the multivariate Cox regression model using enter mode. Results were reported as HR and 95% confidence interval. A $p$-value of less than 0.05 was defined as statistically significant. All statistics were performed using the International Business Machines Corporation Statistical Package for the Social Sciences (IBM SPSS) package 25.0.

## Results

A total of 2984 patients with SpA and 2526 patients with NSBP were included in the analyses. Among the patients with SpA, 1940 (65.0%) had AS, 642 (21.5%) had PsA, 47 (1.6%) had IBD associated SpA, eight (0.3%) had ReA, and six (0.2%) had HLA-B27 associated uveitis. The average duration of follow-up in patients with SpA was 9.1 years, compared with 13.8 years in NSBP. Most (98.7%) of the patients were Chinese. Compared with patients with NSBP, those with SpA were characterized by younger

age, male predominance, shorter duration of follow-up, fewer comorbidities, on more immunosuppressants or at immunosuppressive states, and more long term (>½ year) steroid use. Incidents of CAP requiring hospitalization and severe CAP were similar between the two groups. More patients in the SpA group were eligible for free seasonal influenza vaccines and more patients in the NSBP group were eligible for free pneumococcal vaccines. Details of baseline characteristics are described in Table 1.

### Duration of DMARD use

Sulfasalazine was the DMARD with the longest duration of use. Among all b-DMARDs, infliximab was the drug with the longest duration of use. The average duration of sulfasalazine, etanercept, infliximab, adalimumab, golimumab, and secukinumab use was $5.6 \pm 5.3$, $3.2 \pm 2.8$, $4.1 \pm 4.0$, $2.7 \pm 2.6$, $2.8 \pm 2.3$, and $0.8 \pm 0.6$ years respectively.

### Crude incidence rates and risks of CAP requiring hospitalization/severe CAP

Crude incidence rates of CAP requiring hospitalization and severe CAP in patients with NSBP, patients with SpA, patients with SpA but without use of DMARDs, and patients with SpA but without psoriasis and not taking DMARDs are shown in Table 2. The age adjusted crude incidence rates of CAP in the general population are stated for reference. The crude incidence rates of CAP were the same between the general population and patients with NSBP. Patients with SpA had higher crude incidence rates of CAP requiring hospitalization and severe CAP than patients with NSBP.

Risks of CAP requiring hospitalization and severe CAP in patients with SpA, patients with SpA but without use of DMARDs, and patients with SpA but without psoriasis and not taking DMARDs after propensity score stratification with reference to patients with NSBP are shown in Table 3. When compared with patients with NSBP, the risks of CAP requiring hospitalization in patients with different subgroups of SpA were increased by 2.14–2.64 times. Risks of severe CAP in patients in different subgroups of SpA were also increased by 2.90–4.20 times.

### Risk factors for CAP requiring hospitalization and severe CAP in patients with SpA

In the models of CAP requiring hospitalization, statistically significant ($p < 0.1$) associations in the univariate Cox regression models were age, male gender, smoker, drinker, history of psoriasis, infliximab, use of steroid for >½ year, DM, chronic renal impairment, malignancy, chronic lung disease, chronic heart disease, and cerebrovascular accident. Multivariate Cox regression model showed that infliximab, smoker, history of psoriasis, use of steroid for >½ year, chronic renal impairment, malignancy, and chronic lung disease were independent risk factors for CAP requiring hospitalization in patients with SpA (Table 4).

In the severe CAP models, univariate Cox regression analyses with statistically significant ($p < 0.1$) associations were age, male gender, smoker, drinker, use of steroid for >½ year, chronic renal impairment, malignancy, and chronic lung disease. Multivariate Cox regression analysis showed use of steroid for >½ year, chronic renal impairment, and malignancy were independent risk factors for severe CAP in patients with SpA (Table 5).

### Micro-organisms identified from respiratory specimens

Figure 1 shows the percentage of micro-organisms identified from respiratory specimens. Micro-organisms could be found in 69/183 (37.7%) of patients with SpA and CAP requiring hospitalization, and in 47/138 (34.1%) patients with NSBP and CAP. The three most common micro-organisms identified were *influenzae*, *H. influenzae*, and pneumococcus in both groups. The micro-organisms identified were compatible between the two groups. There were no differences in the percentages of patients identified with pneumococcus and influenza between the two groups (Table 1).

### Missing values

The centralized electronic database in CMS provided very comprehensive clinical information on patients with SpA and NSBP. However, in 161 patients (51 with SpA and 110 with NSBP), no smoking and drinking status had been recorded. The population with missing values represented 2.9% of the studied population.

**Table 1.** Baseline characteristics of patients with SpA and NSBP.

| | Patients with SpA *n* = 2984 | Patients with NSBP *n* = 2526 | *p*-value |
|---|---|---|---|
| Age, years | 49.6 ± 14.4 | 62.1 ± 15.0 | <0.001 |
| Chinese ethnicity | 2954/2984 (99.0%) | 2487/2526 (98.5%) | 0.07 |
| Male gender | 2035/2984 (68.2%) | 912/2526 (36.1%) | <0.001 |
| Study duration, years | 9.06 ± 5.88 | 13.80 ± 5.77 | <0.001 |
| Smoker | 879/2933 (30.0%) | 450/2416 (18.6%) | <0.001 |
| Drinker | 240/2933 (8.2%) | 155/2416 (6.4%) | 0.01 |
| Pneumonia requiring hospitalization | 183/2984 (6.1%) | 138/2526 (5.5%) | 0.29 |
| Severe pneumonia | 22/2984 (0.7%) | 11/2526 (0.4%) | 0.15 |
| Diabetes mellitus | 271/2984 (9.1%) | 394/2526 (15.6%) | <0.001 |
| Chronic renal impairment (stage 3 or above) | 187/2984 (6.3%) | 329/2526 (13.0%) | <0.001 |
| Stage 1 | 2417/2984 (81.0%) | 1446/2526 (57.2%) | |
| Stage 2 | 382/2984 (12.8%) | 753/2526 (29.8%) | |
| Stage 3 | 152/2984 (5.1%) | 285/2526 (11.3%) | |
| Stage 4 | 19/2984 (0.6%) | 34/2526 (1.3%) | |
| Stage 5 | 14/2984 (0.5%) | 8/2526 (0.3%) | |
| Concomitant malignancy | 115/2984 (3.9%) | 227/2526 (9.0%) | <0.001 |
| Chronic lung disease | 98/2984 (3.3%) | 129/2526 (5.1%) | 0.001 |
| Chronic heart disease | 196/2984 (6.6%) | 309/2526 (12.2%) | <0.001 |
| Other immunosuppressants or immune-suppressed states | 835/2984 (28.0%) | 89/2526 (3.5%) | <0.001 |
| History of cerebrovascular accident | 104/2984 (3.5%) | 89/2526 (3.5%) | 0.94 |
| Use of steroid for >½ year | 156/2984 (5.2%) | 10/2526 (0.4%) | <0.001 |
| History of psoriasis | 643/2984 (21.5%) | NA | NA |
| History of inflammatory bowel disease | 47/2984 (1.6%) | NA | NA |
| On sulfasalazine | 1286/2984 (43.1%) | NA | NA |
| On etanercept | 273/2984 (9.1%) | NA | NA |
| On infliximab | 106/2984 (3.6%) | NA | NA |
| On adalimumab | 243/2984 (8.1%) | NA | NA |
| On golimumab | 197/2984 (6.6%) | NA | NA |
| On certolizumab | 40/2984 (1.3%) | NA | NA |
| On secukinumab | 71/2937 (2.4%) | NA | NA |
| Eligible for free seasonal influenza vaccine | 2528/2984 (84.7%) | 2083/2526 (82.5%) | 0.02 |
| Eligible for free pneumococcal vaccine | 485/2984 (16.3%) | 1139/2526 (45.1%) | <0.001 |
| Pneumococcus identified from respiratory specimens | 13/2984 (0.4%) | 5/2526 (0.2%) | 0.12 |
| Influenza identified from respirator specimens | 17/2984 (0.6%) | 12/2526 (0.5%) | 0.63 |

*n*, number; NA, not available; NSBP, non-specific back pain; SpA, spondyloarthritis.

**Table 2.** Crude incidence rates of community-acquired pneumonia.

| | Patients with SpA | Patients with NSBP | General population age 50–64 years[16] |
|---|---|---|---|
| Number of community-acquired pneumonia | 183 | 138 | |
| Patient-years | 27,035.0 | 34,858.8 | |
| Incidence per 1000 patient-years | 6.8 | 4.0 | 4.0 |
| | Patients with SpA but without use of DMARDs | | |
| Number of community-acquired pneumonia | 85 | | |
| Patient-years | 8959.9 | | |
| Incidence per 1000 patient-years | 9.5 | | |
| | Patients with SpA but without psoriasis and not taking DMARDs | | |
| Number of community-acquired pneumonia | 65 | | |
| Patient-years | 7467.7 | | |
| Incidence per 1000 patient-years | 8.7 | | |

DMARD, disease modifying anti-rheumatic drug; NSBP, non-specific back pain; SpA, spondyloarthritis.

**Table 3.** Risk of CAP requiring hospitalization and risk of severe CAP requiring ICU admission or resulting in death determined by propensity score stratification in different subgroups of SpA.

| | CAP requiring hospitalization | | Severe CAP requiring ICU admission or resulting in death | |
|---|---|---|---|---|
| | HR (95% CI) | *p*-value | HR (95% CI) | *p*-value |
| All patients with SpA *versus* patients with NSBP, *n* = 5349 | | | | |
| Patients with NSBP, *n* = 2416 | 1 (reference) | NA | 1 (reference) | NA |
| Patients with SpA, *n* = 2933 | 2.14 (1.71; 2.68) | <0.001 | 2.90 (1.39; 6.06) | 0.01 |
| Patients with SpA but without use of DMARDs *versus* patients with NSBP, *n* = 3466 | | | | |
| Patients with NSBP, *n* = 2416 | 1 (reference) | NA | 1 (reference) | NA |
| Patients with SpA but not on DMARDs, *n* = 1096 | 2.64 (2.00; 3.47) | <0.001 | 3.46 (1.49; 8.01) | 0.004 |
| Patients with SpA but without psoriasis and not taking DMARDs *versus* patients with NSBP, *n* = 3355 | | | | |
| Patients with NSBP, *n* = 2416 | 1 (reference) | NA | 1 (reference) | NA |
| Patients with SpA but without psoriasis and not taking DMARDs, *n* = 939 | 2.38 (1.76; 3.20) | <0.001 | 4.20 (1.81; 9.78) | 0.001 |

Factors matched: age, sex, smoker, drinker, diabetes mellitus, chronic renal impairment, malignancy, chronic lung disease, chronic heart disease, other immunosuppressants or immunosuppressive states, cerebrovascular disease, steroid usage for more than 6 months.
CAP, community-acquired pneumonia; CI, confidence interval; DMARD, disease modifying anti-rheumatic drug; HR, hazard ratio; ICU, intensive care unit; *n*, number; NA, not available; NSBP, non-specific back pain; SpA, spondyloarthritis.

**Table 4.** Univariate and multivariate Cox regression models of CAP requiring hospitalization.

| Characteristics | Patients with pneumonia | Univariate Cox regression models | | Multivariate Cox regression | |
|---|---|---|---|---|---|
| | | Hazard ratio (95% CI) | *p*-value | Hazard ratio (95% CI) | *p*-value |
| Age, *n* = 2984 | | 1.02 (1.02; 1.04) | <0.001 | 1.00 (0.98; 1.01) | 0.83 |
| Chinese ethnicity | 183/2954 (6.2%) | 20.26 (0.00; 254,117.50) | 0.53 | | |
| Male gender, *n* = 2984 | 140/2035 | 1.49 (1.06; 2.10) | 0.02 | 1.28 (0.87; 1.89) | 0.20 |
| Smoker, *n* = 2933 | 90/879 | 2.21 (1.65; 2.95) | <0.001 | 1.68 (1.20; 2.36) | 0.003 |
| Drinker, n = 2833 | 34/240 | 2.58 (1.77; 3.74) | <0.001 | 1.38 (0.90; 2.10) | 0.14 |
| History of psoriasis, *n* = 2984 | 68/643 | 1.57 (1.15; 2.15) | 0.004 | 1.67 (1.19; 2.33) | 0.003 |
| History of inflammatory bowel disease, *n* = 2984 | 1/47 | 0.33 (0.05; 2.36) | 0.27 | | |
| Sulfasalazine, *n* = 2984 | 63/1286 | 1.11 (0.81; 1.51) | 0.52 | | |
| Etanercept, *n* = 2984 | 5/273 | 1.13 (0.45; 2.75) | 0.82 | | |
| Infliximab, *n* = 2984 | 5/106 | 2.12 (0.87; 5.19) | 0.10* | 2.55 (1.04; 6.32) | 0.04 |
| Adalimumab, *n* = 2984 | 6/243 | 1.88 (0.82; 4.32) | 0.14 | | |
| Golimumab, *n* = 2984 | 2/197 | 0.74 (0.18; 3.03) | 0.68 | | |
| Certolizumab, *n* = 2984 | 1/40 | 3.79 (0.52; 27.71) | 0.19 | | |
| Secukinumab, *n* = 2937 | 1/71 | 5.42 (0.71; 41.19) | 0.10** | | |
| Use of steroid for >½ year, *n* = 2984 | 25/156 | 2.37 (1.56; 3.62) | <0.001 | 1.94 (1.25; 3.00) | 0.003 |
| Diabetes mellitus, *n* = 2984 | 27/271 | 1.45 (0.96; 2.18) | 0.07 | 0.79 (0.50; 1.24) | 0.3 |
| Chronic renal impairment, *n* = 2984 | 44/187 | 3.48 (2.47; 4.89) | <0.001 | 1.89 (1.27; 2.82) | <0.001 |
| Malignancy, *n* = 2984 | 33/115 | 4.72 (3.24; 6.88) | <0.001 | 2.89 (1.88; 4.44) | <0.001 |
| Chronic lung disease, *n* = 2984 | 37/98 | 6.54 (4.56; 9.38) | <0.001 | 4.83 (3.26; 7.15) | <0.001 |
| Chronic heart disease, *n* = 2984 | 34/196 | 2.36 (1.62; 3.43) | <0.001 | 1.13 (0.73; 1.76) | 0.58 |
| Other immunosuppressants or immune-suppressed states, *n* = 2984 | 51/835 | 0.81 (0.59; 1.12) | 0.21 | | |
| Cerebrovascular accident, *n* = 2984 | 24/104 | 2.72 (1.77; 4.18) | <0.001 | 1.25 (0.74; 2.13) | 0.41 |

*$p < 0.100$.
**$p > 0.100$.
CAP, community-acquired pneumonia; CI, confidence interval; *n*, number.

**Table 5.** Univariate and multivariate Cox regression models of severe CAP.

| Characteristics | Patients with severe pneumonia | Univariate Cox regression models | | Multivariate Cox regression | |
|---|---|---|---|---|---|
| | | Hazard ratio (95% CI) | *p*-value | Hazard ratio (95% CI) | *p*-value |
| Age, *n* = 2984 | | 1.03 (1.00; 1.06) | 0.05 | 1.00 (0.97; 1.04) | 0.83 |
| Chinese ethnicity, *n* = 2984 | 22/2954 (0.7%) | 20.26 (0.00; 7.46E+12) | 0.83 | | |
| Male gender, *n* = 2984 | 19/2035 (0.9%) | 2.91 (0.86; 9.83) | 0.09 | 2.13 (0.56; 8.06) | 0.27 |
| Smoker, *n* = 2933 | 13/879 (1.5%) | 3.35 (1.43; 7.84) | 0.01 | 1.77 (0.66; 4.73) | 0.26 |
| Drinker, *n* = 2833 | 7/240 (2.9%) | 5.27 (2.15; 12.92) | <0.001 | 2.44 (0.88; 6.79) | 0.09 |
| History of psoriasis, *n* = 2984 | 4/643 (0.6%) | 0.75 (0.25; 2.22) | 0.61 | | |
| History of inflammatory bowel disease, *n* = 2984 | 0/47 (0.0%) | 0.05 (0.00; 113,066.18) | 0.69 | | |
| Sulfasalazine, *n* = 2984 | 8/1286 (0.8%) | 0.58 (0.24; 1.39) | 0.22 | | |
| Etanercept, *n* = 2984 | 0/273 (0.0%) | 0.05 (0.00; 4857.80) | 0.60 | | |
| Infliximab, *n* = 2984 | 0/106 (0.0%) | 0.05 (0.00; 790,687.09) | 0.71 | | |
| Adalimumab, *n* = 2984 | 0/243 (0.0%) | 0.05 (0.00; 36,198.81) | 0.66 | | |
| Golimumab, *n* = 2984 | 0/197 (0.0%) | 0.05 (0.00; 117,553.70) | 0.68 | | |
| Certolizumab, *n* = 2984 | 0/40 (0.0%) | 0.05 (0.00; 1.15E+20) | 0.91 | | |
| Secukinumab, *n* = 2937 | 0/71 (0.0%) | 0.05 (0.00; 9.84E+53) | 0.96 | | |
| Use of steroid for >½ year, *n* = 2984 | 4/156 (2.6%) | 3.36 (1.13; 9.96) | 0.03 | 3.24 (1.05; 9.98) | 0.04 |
| Diabetes mellitus, *n* = 2984 | 4/271 (1.5%) | 1.89 (0.64; 5.58) | 0.25 | | |
| Chronic renal impairment, *n* = 2984 | 8/187 (4.3%) | 6.46 (2.70; 15.47) | <0.001 | 3.12 (1.13; 8.62) | 0.03 |
| Malignancy, *n* = 2984 | 6/115 (5.2%) | 8.06 (3.15; 20.61) | <0.001 | 4.02 (1.36; 11.90) | 0.01 |
| Chronic lung disease, *n* = 2984 | 4/98 (4.1%) | 5.64 (1.91; 16.68) | 0.002 | 2.61 (0.82; 8.30) | 0.10 |
| Chronic heart disease, *n* = 2984 | 2/196 (1.0%) | 1.06 (0.25; 4.55) | 0.94 | | |
| Other immunosuppressants or immune-suppressed states, *n* = 2984 | 6/835 (0.7%) | 0.80 (0.31; 2.04) | 0.63 | | |
| Cerebrovascular accident, *n* = 2984 | 2/104 (1.9%) | 1.84 (0.43; 1.89) | 0.41 | | |

CAP, community-acquired pneumonia; CI, confidence interval; *n*, number.

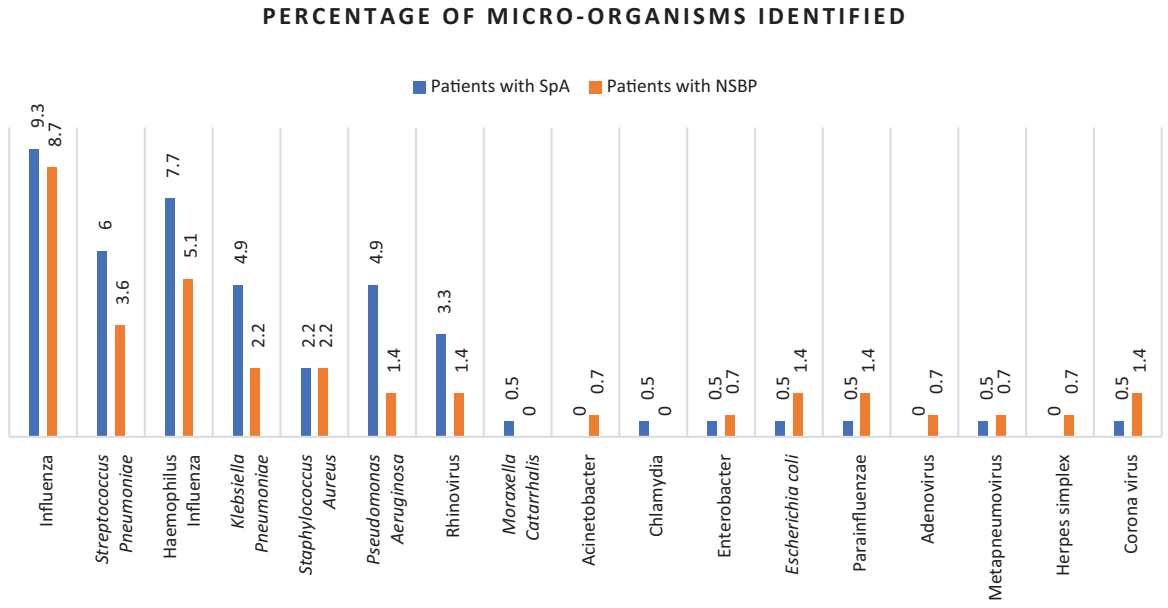


**Figure 1.** Micro-organisms identified from respiratory specimens from patients with community-acquired pneumonia requiring hospitalization.
NSBP, non-specific back pain; SpA, spondyloarthritis.

## Discussion

Patients with SpA had increased risk of both CAP requiring hospitalization and severe CAP. Infliximab was the only DMARD found to be independently associated with CAP requiring hospitalization. Smoking and long-term use of steroids were potentially avoidable risk factors.

Influenza and pneumococcal vaccinations are the two most effective strategies in prevention of CAP in patients with SpA. Vaccination programs vary between countries, ranging from universal vaccination to age-based or risk-based stratification. The 2019 European League Against Rheumatism (EULAR) recommends consideration of influenza and pneumococcal vaccination for the majority of patients with autoimmune inflammatory rheumatic diseases.[17] The increased risk of severe CAP in patients with SpA demonstrated in this study supports these recommendations.

The most ideal controls would be the general population; however, such data are unavailable in hospital-based records. Patients with NSBP were chosen as a surrogate clinical control group because of their immunocompetence and absence of specific risk factors for CAP. In spite of that, crude incidence rates of CAP in patients with NSBP and the age adjusted population were the same. Potential confounding factors were also eliminated by their inclusion in the propensity score stratification model.

A two-fold increased risk of CAP requiring hospitalization and severe CAP was found in patients with SpA after adjusting for potential confounding factors, and excluding patients on DMARDs and psoriasis. From the results of the three-propensity score adjusted subgroups, the increased risk of CAP in SpA was genuine and unrelated to the effect of DMARDs. Our cohort was characterized by known poor prognostic factors, including predominance of males,[18] smokers,[19,20] and long disease duration, which presupposed a certain degree of spinal deformity, and functional and respiratory impairment. Previous prospective studies in the same patient group[21,22] showed a moderate degree of functional impairment and decreased spinal mobility. The resultant restriction in chest movement hinders the expulsion of respiratory secretions, which could partly explain an increased risk of CAP.[23] Furthermore, disease activity could be another contributing factor to CAP. Despite a lack of data in patients with SpA, studies have consistently shown higher risk of respiratory infection in patients with high disease activity in rheumatoid arthritis (RA).[24,25] A similar relationship could be present in patients with SpA.

Infliximab was singled out from the multivariate Cox regression model as the only anti-TNF drug associated with CAP hospitalization. Its unique pharmacokinetics of high peak-drug concentrations up to a level 50 times higher than median-trough

concentrations[26,27] may be a distinguishing susceptibility to CAP infections. As studies in SpA are sparse, a similar study in RA also demonstrated an association between anti-TNF therapy and influenza in the general population.[28] A previous RCT of patients with AS on anti-TNF therapy found low risk of serious infections.[4] However, the population studied was highly selective with short duration of follow-up. A Canadian observational cohort of 440 patients with axial SpA found increased serious infections in c-DMARDs use, but not anti-TNF use.[29] In this study, no association was found between b-DMARDs and severe CAP but the number of events was small and may not have had adequate power to conclude.

Potentially preventable risk factors for CAP were smoking and steroid use for >½ year. Cigarette smoking contributes to significant morbidity in SpA as manifested by worsening in all the following areas of disease activity:[30,31] physical mobility,[19,32] functional limitation,[33] structural damages,[34,35] quality of life,[19] and bronchopulmonary and cardiovascular outcomes[36] in European as well as in local data.[37] The additional risk of CAP in smokers lends further urgency to rheumatologists in promoting smoking cessation in patients with SpA. Risk factors for CAP in patients with SpA were similar to those found in the general population.[8–12,15] Psoriasis was also one of the risk factors compatible with the international study.[38]

Long-term use of corticosteroids in patients with SpA is not recommended by any guidelines, including the Assessment of SpondyloArthritis international Society-EULAR recommendations,[39] the American College of Rheumatology,[40] and the Asia-Pacific League of Associations for Rheumatology,[41] due to their long-term side effects.[42] Short-term use of high dose prednisolone improved outcomes in AS in a small, double-blind RCT.[43] The duration of steroid therapy is a clinical decision with adequate consideration of risks and benefit.

Influenza,[44] streptococcus pneumonia,[44–49] and haemophilus influenza[46,49] were overall the most common microbiological pathogens identified from respiratory specimens in this study. The types of microorganism and prevalence were compatible with other international studies.[46,47] Identification of microbiological pathogens in respiratory specimens and blood cultures aids diagnosis and guides antibiotics treatment in moderate to severe CAP in accordance with international guidelines.[45]

CAP due to influenza and streptococcus pneumonia are preventable with appropriate vaccination. Our analyses did not include data on influenza and pneumococcal vaccinations status. Although more patients with SpA were eligible for free seasonal influenza vaccines and more patients with NSBP were eligible for free pneumococcal vaccines, patients identified with the two organisms were similar between the two groups. The data therefore suggested that the increase in CAP was unlikely related to the vaccination policy.

### *Limitations*

Some limitations are noteworthy. The use of patients with NSBP as a surrogate control group for the general population may contribute to bias; however, the hospital electronic records allowed identification and elimination of most of the identified confounding factors. Missing records of smoking and drinking status constituted 2.9% of the studied population and could be considered as insignificant. DMARDs other than the ones we mentioned were also uncollected. Since there is no International Classification of Disease code for SpA, we attempted to go through all electronic records manually for disease diagnosis. In addition, we also went through all hospitalization records to ensure that all admissions due to CAP were recorded.

Despite the large studied population, the number of patients treated with b-DMARDs was small. A limitation of the retrospective design was the lack of information on the activity and chronicity of disease which may contribute to the risk of CAP. There were other confounding factors we failed to mention, for example, Parkinson's disease and dementia. Future study in these areas could provide valuable information concerning the effect of tight disease control on prevention of CAP.

### *Conclusion*

The risk of CAP is increased in all patients with SpA. Universal influenza and pneumococcal vaccination are favored, and smoking cessation and avoidance of long-term use of steroid use are recommended to reduce the risk of CAP.

## Conflict of interest statement

The authors declare that there is no conflict of interest.

## Ethics statement

The study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (reference number UW 18-263) and local ethics committees. It was conducted in accordance with the Declaration of Helsinki and the guidance of Good Clinical Practice, 30 November 2006. The Institutional Review Board also waived the need for informed consent since personal information had been de-identified in our study.

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