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Characteristics of hospital admissions for pneumonia in HIV-positive individuals in Winnipeg, Manitoba: a cross-sectional retrospective analysis

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Abstract

Lung infection in human immunodeficiency virus (HIV)-positive individuals remains an important cause of morbidity and mortality, even in the current antiretroviral therapy era. Pneumonia is the most common cause of admission in HIV-positive individuals in our centre as reported in a previously published study. The objective of this retrospective observational study was to further characterize these admissions, with respect to index of disease severity at presentation, organisms identified, and investigations pursued including bronchoalveolar lavage (BAL). There were 123 unique patients accounting for a total of 209 admissions from 2005 to 2015. An organism was isolated in only 33% of all admissions (68/209). The most common organism was *Pneumocystis jirovecii* with a frequency of 29% of all admissions. Eighty-seven percent of presentations were mild, and 13% were moderate by CURB-65 criteria. A total of 39 BALs were performed, of which 27 yielded an organism (69%). Considering the burden of disease, low diagnostic yield of the current diagnostic strategy and increased morbidity and mortality caused by pneumonia in HIV-positive individuals, further methods are needed to more accurately target therapy. The preponderance of mild disease in this study suggests that better diagnostic tests may identify individuals that can be candidates for outpatient therapy.

Keywords

Human immunodeficiency virus, pneumonia, bronchoalveolar lavage, CURB-65, immunocompromised, Canada

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Introduction

Lung infection in human immunodeficiency virus (HIV)-positive individuals remains an important cause of morbidity and mortality. Although the advent of antiretroviral therapy (ART) has decreased the risk dramatically, it remains approximately 20 times higher than general population.[1,2] Late presentation with advanced immune deficiency is seen in the Canadian prairies and contributes to the greater susceptibility to pneumonia.[3] Recurrent pneumonia is an AIDS-defining condition, as it is considered an indicator of immunosuppression.[4] Furthermore, pneumonia is a common cause of hospital admission amongst individuals with HIV, and is the most common cause of admission in our centre as reported in a previously published study.[5,6]

The causative organisms often depend on CD4 cell counts, hence the optimal empiric therapy to use for community-acquired pneumonia in the HIV population varies. Reports in the literature vary on the distribution of causative organisms by geography; many focus specifically on bacterial, pneumocystis or tuberculosis epidemiology only, and some include nosocomial pneumonia.[5,7–9] Vélez et al. reported the development of a protocol for bronchoalveolar lavage (BAL) of patients

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with HIV admitted with pneumonia to optimize empiric treatment guidelines.[10] This strategy to identify etiologic agents has been implemented in their centre in Colombia, but has not yet been widely adopted elsewhere and has been recommended only in cases of treatment failure.[11,12] Even a prospective study from the USA specifically undertaken to identify risk factors for specific pulmonary pathogens with the use of extensive testing only utilized BAL in 48 of 230 admissions.[13] In addition, relying on serological tests for atypical causative agents may be hampered by advanced immunosuppression.

It is also unclear as to how index of pneumonia severity scores such as CURB-65 and Pneumonia Severity Index (PSI) developed in the general population may apply to the HIV-positive population.[12,14] Studies published by different groups worldwide have assessed the validity of these scores with mixed results, and some have also suggested new, heterogeneous criteria (such as CD4 cell count) for admission that require further studies for consensus.[7,8,15]

The objective of the present study was to further characterize pneumonia admissions for HIV-positive individuals in our centre, with respect to index of disease severity at presentation, organisms identified, investigations pursued including BAL, and initial choice of therapy. Data were analyzed to determine the yield of BAL in cases in which it was performed to explore if there may be benefit from promoting regular BAL for these admissions.

Methods

The Winnipeg Regional Health Authority Medical Database was used to identify all admissions of HIV-positive patients admitted to medical wards with a diagnosis of pneumonia from January 2005 to January 2015 in one Winnipeg tertiary care hospital. Patients were not required to provide informed consent. Admission diagnosis of pneumonia was at the discretion of the admitting physician. Patient demographics and length of stay were obtained through the Medical Database, and an Internal Medicine resident obtained clinical information through hospital chart reviews. Initial search of the Medical Database yielded 389 admissions. After missing, incorrectly coded and duplicated records were accounted for, a total of 209 admissions were analyzed in this study. In addition to hospital charts, data regarding date of diagnosis and death were collected from clinic records kept by the Manitoba HIV Program.

Of note, the decision to proceed with BAL was at the discretion of the treating primary physicians and consultant physicians. Standard microbiological studies in our centre include bacterial, viral, fungal and acid-fast bacilli culture as well as cytology for *Pneumocystis jirovecii* pneumonia (PJP) and polymerase chain reaction (PCR) for viruses.

The data collected for the CURB-65 criteria were further categorized into "Mild" for a score of 0–1, "Moderate" for a score of 2–3, and "Severe" for a score of 4–5.[12] We collected data on the initial antibiotic administered in the emergency room setting for each admission. This data for whether or not "Initial Therapy Followed IDSA Guidelines" refers to the 2007 Infectious Diseases Society of America (IDSA) Guidelines for treatment of Community Acquired Pneumonia (CAP). The guidelines recommend a respiratory fluoroquinolone or a beta-lactam plus a macrolide or doxycycline as initial therapy.[16]

Data were collected using Excel software and analyzed using SPSS. Independent T-test was used to compare length of stay among the groups with various CD4 cell counts and ART treatment.

Results

Patient and admission characteristics

A total of 209 admissions were analyzed for the data available. Females accounted for 48% of all admissions. The average age at time of admission was 42 years (standard deviation [SD] = 9). The median CD4 cell count for 188/209 (90%) admissions was 111 cells/mm^3 (Q1 to Q3 = 27 to 297). For the admissions where CD4 cell count was available, 118/188 (63%) had a count of < 200 cells/mm^3, 55/188 (29%) had a count of ≤ 200 to ≥ 500 cells/mm^3, and 15/188 (8%) had a count of > 500 cells/mm^3. Only 97/203 (48%) patients were on ART at the time of admission. The median length of stay was five days (Q1 to Q3 = 3 to 11). Length of stay is further characterized by ART status and CD4 cell count in Table 1. There was a statistically significant difference between length of stay between patients on ART or not, as well as CD4 < 200 or CD4 ≥ 200 ($p = 0.022$ and 0.015, respectively). New diagnosis of HIV occurred in seven admissions. The remaining 163 admissions where duration of HIV diagnosis information was available showed a median duration of diagnosis of eight years (Q1 to Q3 = 3 to 14).

There were 123 unique patients comprising the total 209 admissions. The average number of admissions per patient was 1.7 (SD = 2.2, range = 1 to 17). Thirty-two of the 123 unique patients (26%) were deceased at time of data collection and of these, date of death was available for 24. Eight people died during their admission for pneumonia, five people died within one year of admission, six people died within two years of admission, four people within four years of admission, and

one person died within five years of admission. Of the 24 deceased patients where date of death was available, only nine were recorded as having been on ART. Of those nine, eight patients were consistently recorded as being on ART on single or multiple admissions, and the remaining one patient who was not consistently on ART was recorded as being on ART only 2/7 admissions. The average time from first admission to death during the analyzed time period was one year (SD = 1.31, range = 0 to 4), and the average number of admissions from first admission to death was 1.6 (SD = 1.5, range 1 to 7).

For all unique patients, 78% were smokers and 87% had a history of substance use. Only 15% of patients did not have comorbidities. Patient and admission characteristics are summarized in Table 1.

Table 1. Summary of patient and admission characteristics.

Variables	Frequency (%)
Male	109/209 (52%) admissions
Female	100/209 (48%) admissions
History of substance use	102/117 (87%) admissions
History of IDU	48/117 (41%) admissions
History of tobacco use	83/106 (78%) patients
On ART	97/203 (48%) admissions
	Average*/Median (SD/IQR)
Age	42* (9*) years
CD4 cell count	111 (27–297) cells/mm^3
Length of stay	5 (3–11) days
On ART	4 (3–8) days
Not on ART	7 (4–15) days
CD4 < 200	7 (4–16) days
CD4 ≥ 200– ≤ 500	4 (3–9) days
CD4 > 500	4 (3–5) days

ART: antiretroviral therapy; IDU: injecting drug use.

Characteristics of pneumonia

For all admissions, an organism was isolated in only 33% (68/209). The most common organism was *Pneumocystis jirovecii* (29% of admissions with an organism isolated). Specific organisms and frequencies are displayed in Figure 1. The most common organisms in patients with CD4 cell count <200 cells/mm^3 was PJP, with CD4 cell count ≥ 200– ≤ 500 cells/mm^3 was methicillin-resistant *Staphylococcus aureus* (MRSA), and with CD4 cell counts >500 cells/mm^3 was *Streptococcus pneumoniae* (Table 2).

The proportion of method of diagnosis per organism is depicted in Figure 2. A total of 39 BALs were performed, 27 of which yielded an organism (69%). Of 118 individuals with CD4 < 200, 79 did not have bronchoscopy performed (67%). Of note, 18 (86%) PJP admissions were diagnosed via BAL, and 15 (79%) *S. pneumoniae* admissions were diagnosed via blood cultures. Coinfection was detected only with PJP and

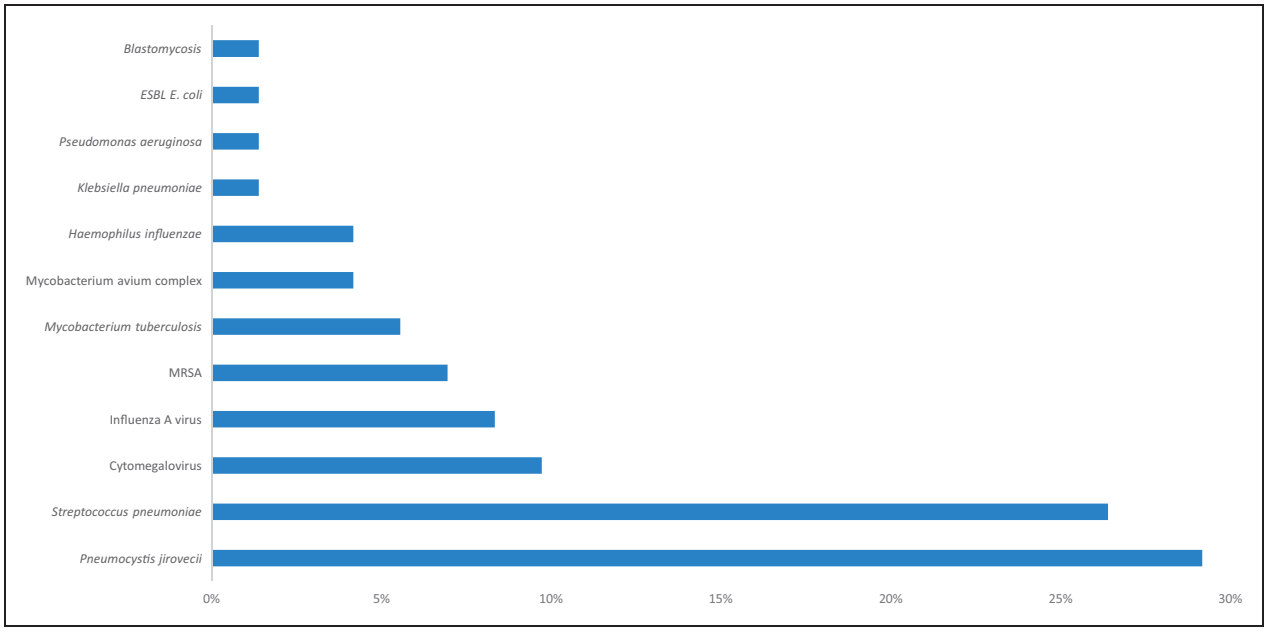

Figure 1. Frequency of organisms identified. MRSA: methicillin-resistant *Staphylococcus aureus*. ESBL: extended spectrum beta-lactamase.

Table 2. Frequency of organisms by CD4 cell count subgroups.[a]

CD4 cell count	<200	≥200–500	>500
Most common	*Pneumocystis jirovecii* (35%)	MRSA (31%)	*Streptococcus pneumonia* (50%) Influenza A virus (50%)
	Streptococcus pneumoniae (27%)	*Streptococcus pneumoniae* (23%)	N/A
	Cytomegalovirus (10%)	Cytomegalovirus (15%)	N/A
	Mycobacterium tuberculosis (6%) Mycobacterium avium complex (6%)	*Pseudomonas aeruginosa* (8%) *Haemophilus influenzae* (8%) Influenza A virus (8%) *Pneumocystis jirovecii* (8%)	N/A
Least common	*Haemophilus influenzae* (4%) Influenza A virus (4%)	NA	NA

MRSA: methicillin-resistant *Staphylococcus aureus*. N/A: not applicable.
[a]More than one organism listed indicates equal frequencies.

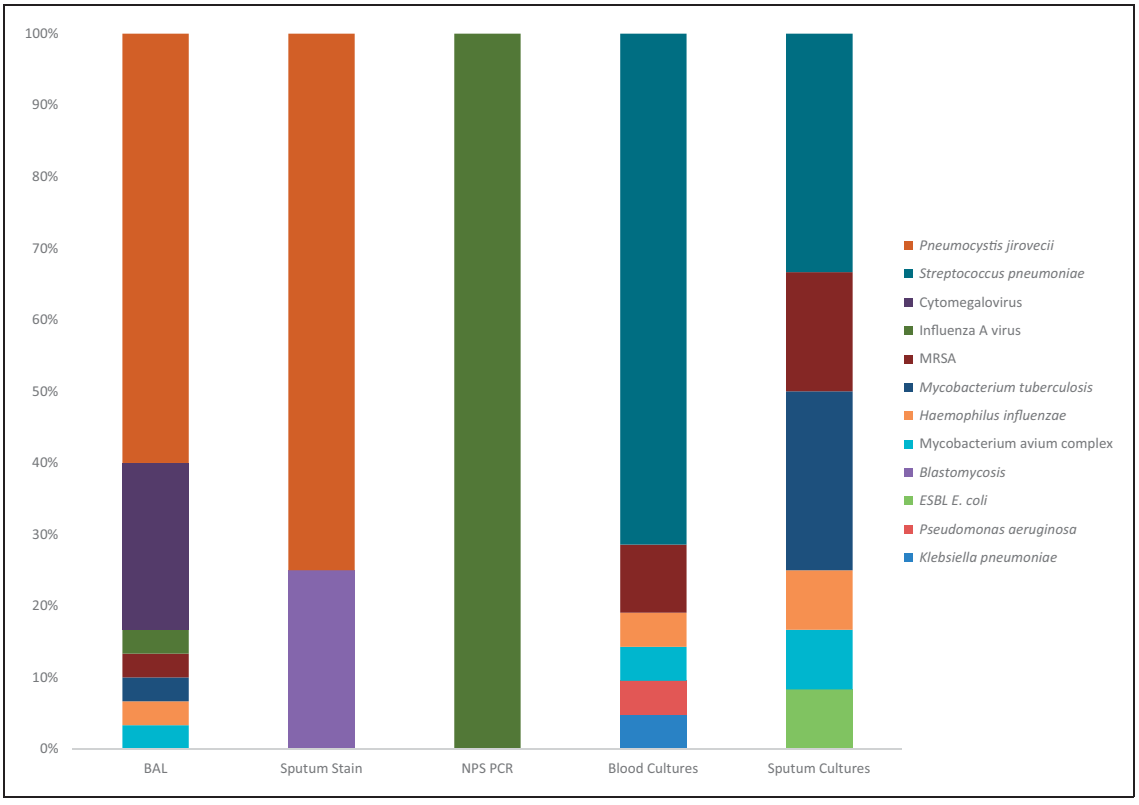

Figure 2. Proportion of method of diagnosis per organism isolated.
BAL: bronchoalveolar lavage; NPS PCR: nasopharyngeal swab polymerase chain reaction.

cytomegalovirus (CMV), where the significance of the latter as a pathogen is questionable.

Index of disease severity

To gauge the severity of pneumonia clinical presentations, we used CURB-65. For all admissions, 87% of presentations were mild, and 13% were moderate. Interestingly, for all 209 admissions, only one of the presentations was severe by the CURB-65 criteria. We analyzed the CURB-65 criteria for each organism isolated (Figure 3). For admissions with a mild CURB-65 score, 70% had no organism isolated, and for admissions with a moderate CURB-65 score, 54% had no organism isolated; these values are excluded from Figure 3 for scaling purposes. The median CD4 cell count for mild CURB-65 was 110 cells/mm^3 (Q1 to Q3 = 23–287), and for moderate CURB-65 was 193

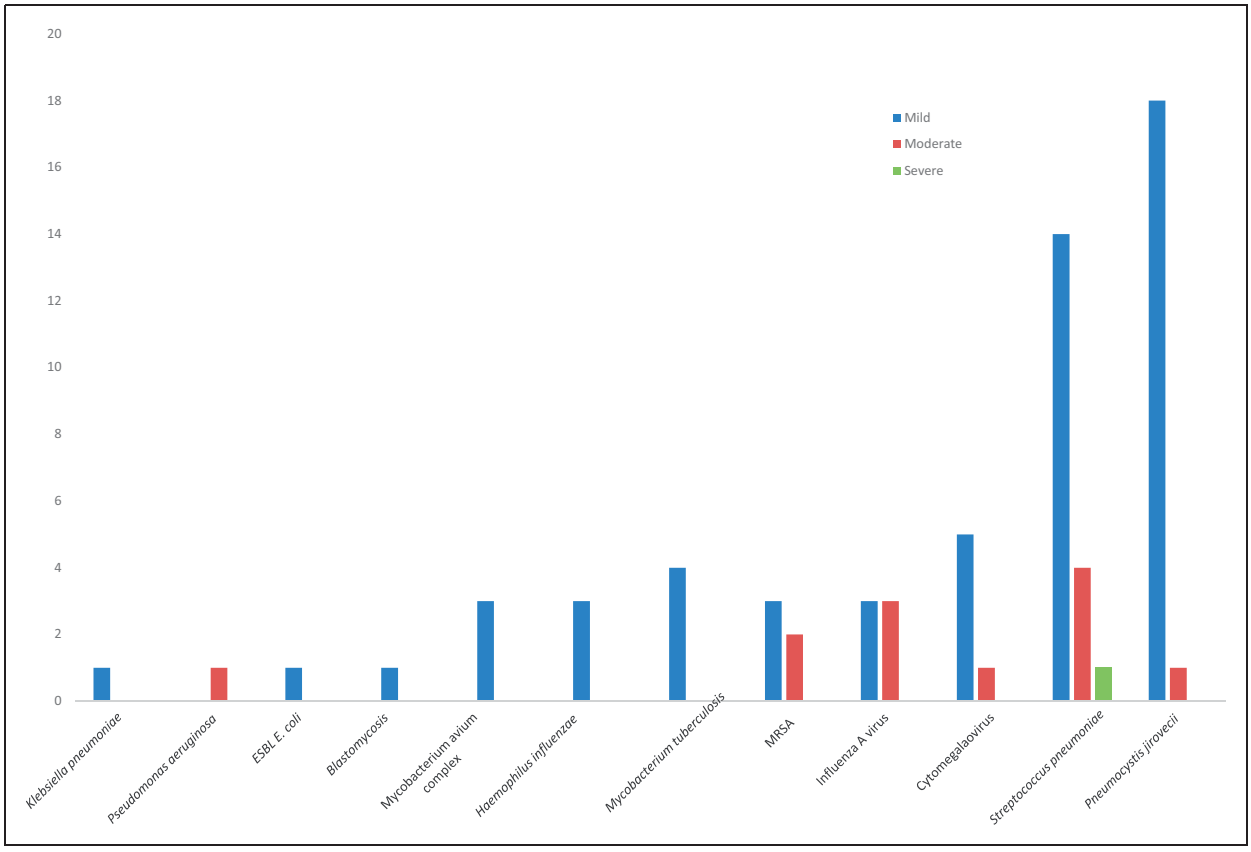

Figure 3. Frequency of CURB-65 severity for each organism. The y-axis represents the total number of admissions in which each organism was isolated.

cells/mm^3 (Q1 to Q3 = 73–390). The median length of stay for mild CURB-65 was six days (Q1 to Q3 = 3 to 10), and for moderate CURB-65 was four days (Q1 to Q3 = 3 to 10.5).

Clinician practices

The initial choice of antibiotic therapy as following IDSA guidelines or not for the 206 admissions where these data were available showed that 68% of physicians followed the IDSA guidelines.

Discussion

For all hospital admissions, there was a low percentage of an isolated organism at only 33%. Overall, the most common organism identified in our study was PJP. This is in keeping with 63% of admissions presenting with CD4 < 200. Only 39 BALs were performed for the 209 admissions, with 27 of these isolating an organism at a yield of 69%, much higher than the overall 33% yield for all admissions. Indeed, general indications for pursuing BAL when basic investigations are not fruitful include non-resolving pneumonia, infiltrates in an immunocompromised host, and exclusion of diagnosable conditions.[17] The low rate of obtaining BAL even in the presence of advanced HIV-induced immunosuppression contributes to low rates of etiological diagnosis.

The literature regarding etiologic agents of pneumonia in HIV-positive individuals varies widely by study design and geography. For example, a study at a single centre in Florida undertaken to examine pulmonary complications of bacterial pneumonia and required that an organism was detected on Gram stain or BAL for inclusion. They also included nosocomial infections. The most common etiologic agent identified was *Pseudomonas aeruginosa*, followed by *S. pneumoniae* and *S. aureus*.[5] Another example is a study from seven centres in the USA spanning from California to New Jersey examining bacterial etiologic agents in HIV-positive individuals found that an organism was isolated in 38.8% of admissions, comparable to our findings. The most common etiologic agents found in these centres combined were *S. pneumoniae, S. aureus* and *Haemophilus influenzae*.[1] Another Californian, albeit smaller, study found similar etiologic agents. The study focused specifically on bacterial CAP, and all organisms were identified via blood or sputum culture.[18] In a Colombian study where all patients had a

BAL performed, an organism was isolated in 65.2% of admissions. The most common agents were mycobacterial, PJP and bacterial pneumonia not further specified.[10] A recently published study from Nepal examined sputum cultures from newly diagnosed HIV-positive individuals and isolated an organism in 70.8% of patients. The most common agents were *Klebsiella pneumoniae*, *Candida albicans* and *Mycobacterium tuberculosis*.[9] A retrospective Canadian study showed that PJP remained a common agent at a frequency of 24%.[19] Information at various geographical sites is difficult to compare due to probable population differences, study design and methods of diagnosis. Our study examines all organisms of CAP discovered by any method of diagnosis. Our infectious aetiology at a single centre in Manitoba appears to be PJP, *S. pneumoniae* and cytomegalovirus. While almost all patients in our cohort had blood cultures collected, and the majority also had a sputum culture, it seems BAL was reserved for only the patients with lower CD4 cell counts. In addition, the lack of identification of atypical bacteria causing CAP (*Legionella pneumophila, Mycoplasma, Chlamydophila*) may be the result of low index of suspicion of these pathogens in HIV-infected individuals, low diagnostic yield of culture and suboptimal performance of serology in HIV with advanced immunosuppression. However, this does not explain the limited number of BALs performed, as the majority of patients admitted had CD4 < 200. Due to the retrospective nature of the study, it was difficult to determine clear or consistent indications as to what prompted further investigation with BAL.

Multiple groups have examined the use of index of disease severity of pneumonia scores such as the PSI and CURB-65 for HIV-positive individuals. These groups suggest a variety of additions to these scoring systems, such as performing a blood culture on all HIV-positive individuals presenting with pneumonia or creating a scoring criterion for CD4 cell counts.[7,8] Two groups – one American and one Portuguese – found PSI or CURB-65 may indeed be valid for predicting mortality and need for hospitalization; the Portuguese study suggested at least bearing in mind the CD4 cell count.[18,20] However, a Canadian group found that CURB-65 may underestimate mortality in this group and advised against using CURB-65 altogether.[21] An American group applied a scoring system called the Veterans Aging Cohort Study (VACS) Index with specific focus on older HIV-positive individuals (age ≥ 50) and 30-day mortality, length of stay and readmission. Other than age, this scoring system is comprised of completely different components than CURB-65 and PSI, including CD4 cell count and viral load. While they found that an increased VACS Index was significantly associated with outcomes, they did not find a difference in outcomes for HIV status when compared to an HIV-uninfected cohort.[22] Not surprisingly in our study the duration of stay was shorter in individuals on ART and those with CD4 ≥ 200. The longer duration of stay results in higher healthcare costs and points to the need for early diagnosis and ART treatment. It is difficult to explain the discrepancy observed between mild and moderate CURB-65 scores regarding CD4 cell count and length of stay, however. A large portion of this cohort had low CD4 cell counts, which may have lowered the threshold for admission. Overall disease severity by CURB-65 was low, especially considering the hospitalization rate. Using the admitting physician's discretion as the diagnostic criteria of pneumonia for this particular database (as opposed to ICD-9 codes for example), may contribute to the overall decreased severity of admissions. There was also a high rate of intravenous drug use in this cohort, perhaps promoting admission in a population at high risk for failure of outpatient treatment. Furthermore, application of CURB-65 criteria to the HIV population is limited by the fact that the patients are almost all less than 65 years old (i.e. there is a point for the scoring system that is rarely met).

Strengths of this study include the duration of ten years for data collection, and the reasonably large sample size. This study also examines all causative organisms including fungal, viral, bacterial and mycobacterial. The weaknesses include the retrospective nature of the data, which relies on hospital clinicians and trainees for accurate record keeping. There are also inherent flaws in creation of the database as indicated by the large number of missing records and incorrectly coded admissions. Also, many data points such as substance use and ART compliance are subjective and may be subject to recall bias. HIV viral loads were available in a small subset, limiting the ability to objectively assess adherence to ART. The study could be further strengthened by the addition of vaccination data, which is a separate database that may be accessed in the future.

The discrepancy in composition of etiologic agents per admission may be explained by the methods of diagnosis or lack thereof; suspicion of an opportunistic infection possibly prompted more tenacity in determining the causative organism and thus the high yield of PJP. Because such a large proportion of admissions had no organism isolated, it would be difficult to determine the etiologic agents in this group of patients, which may have been bacterial infections that were treated empirically or self-limited viral infections. In our centre, BAL is a limited resource as dictated by bronchoscopy suite, respiratory medicine specialist and support staff availability, which likely contributed to the relatively low number of BALs performed.

Considering the burden of disease and increased morbidity and mortality caused by pneumonia in

HIV-positive individuals, further methods are needed to more accurately target therapy. This may include more frequent BALs or other high-throughput methods of sputum analysis. Unfortunately implementing these methods are hindered by lack of funding, staff and laboratory capacity including molecular diagnostics for PJP, which are unavailable in our centre. Perhaps future studies would help bolster the need for increased diagnostic methods in this population.

Declaration of conflicting interests

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