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TITLE:
Prevalence and Etiology of Community-acquired Pneumonia in Immunocompromised Patients

ABSTRACT:
BACKGROUND: The correct management of immunocompromised patients with pneumonia is debated. We evaluated the prevalence, risk factors, and characteristics of immunocompromised patients coming from the community with pneumonia. METHODS: We conducted a secondary analysis of an international, multicenter study enrolling adult patients coming from the community with pneumonia and hospitalized in 222 hospitals in 54 countries worldwide. Risk factors for immunocompromise included AIDS, aplastic anemia, asplenia, hematological cancer, chemotherapy, neutropenia, biological drug use, lung transplantation, chronic steroid use, and solid tumor. RESULTS: At least 1 risk factor for immunocompromise was recorded in 18% of the 3702 patients enrolled. The prevalences of risk factors significantly differed across continents and countries, with chronic steroid use (45%), hematological cancer (25%), and chemotherapy (22%) the most common. Among immunocompromised patients, community-acquired pneumonia (CAP) pathogens were the most frequently identified, and prevalences did not differ from those in immunocompetent patients. Risk factors for immunocompromise were independently associated with neither Pseudomonas aeruginosa nor non–community-acquired bacteria. Specific risk factors were independently associated with fungal infections (odds ratio for AIDS and hematological cancer, 15.10 and 4.65, respectively; both P = .001), mycobacterial infections (AIDS; P = .006), and viral infections other than influenza (hematological cancer, 5.49; P < .001). CONCLUSIONS: Our findings could be considered by clinicians in prescribing empiric antibiotic therapy for CAP in immunocompromised patients. Patients with AIDS and hematological cancer admitted with CAP may have higher prevalences of fungi, mycobacteria, and noninfluenza viruses.

Study Design and Population ::: MATERIALS AND METHODS:
This is a secondary analysis of the Global Initiative for MRSA Pneumonia (GLIMP) database [10]. The GLIMP study was an international, multicenter, observational, point-prevalence study of adult patients hospitalized for community-onset pneumonia in 54 countries worldwide. Patients were enrolled on a single day during the months of March, April, May, and June 2015. The methods of the GLIMP study have been published elsewhere [10]. The coordinating center (University of Texas Health Science Center, San Antonio) received approval from its institutional review board (No. HSC20150184E).
All adult patients (aged >18 years old) coming from the community and hospitalized with pneumonia during study period were included. Pneumonia was defined as the presence of a new pulmonary infiltrate on chest radiograph at the time of hospitalization, associated with ≥1 of the following criteria: (1) new or increased cough with/without sputum production and/or purulent respiratory secretions, (2) fever or hypothermia, and (3) evidence of systemic inflammation (ie, abnormal white blood cell count or increased C-reactive protein or procalcitonin level). Hospitalized patients with a diagnosis of hospital-acquired or ventilator-associated pneumonia were excluded.

Data Collection ::: MATERIALS AND METHODS:
Data were collected from medical records at the time of hospital admission. Data gathered included demographics; respiratory and cardiovascular comorbid conditions; immunocompromised status and other chronic medical conditions; severity of pneumonia (defined as either intensive care unit admission, use of invasive or noninvasive mechanical ventilation, or use of vasopressors/inotropes during the first 24 hours after hospital admission); and specific risk factors for resistant pathogens infection, including chronic aspiration, being bedridden, malnutrition, presence of enteric tube feeding and indwelling catheters (including central venous and urinary catheters), previous infections, chronic microbial colonization, and previous healthcare exposures. The number and type of microbiological samples obtained within 24 hours after hospital admission were also collected. Culture-positive tests, kind of sample, and antibiotic resistance patterns were also gathered, along with empiric antibiotic treatment, given within 24 hours after hospital admission.

Microbiological Workup ::: MATERIALS AND METHODS:

Diagnostic testing was performed according to local standard operating procedures and included collection of respiratory and blood cultures and testing for urinary antigens. Microbiological examinations and susceptibility testing were performed according to local standard protocols within the first 24 hours after hospital admission [11]. Multivariable logistic regression models were performed for patients who had a positive culture, to identify specific risk factors for single pathogens.
Causative pathogens were stratified according to the coverage of standard therapy for community-acquired pneumonia (CAP) [5–7]. Those not covered by standard CAP therapy included the following: non–community-acquired bacteria (Acinetobacter baumanii, Enterococcus vancomycin-resistant, Nocardia spp.), mycobacteria, fungi (Aspergillus fumigatus, Coccidioides, Criptococcus, Pneumocystis jirovecii), and viruses other than influenza [5–7]. Those covered by standard CAP therapy included Pseudomonas aeruginosa, methicillin-resistant Staphylococcus aureus, methicillin-sensitive S. aureus, Enterobacter spp., Enterococcus spp., Escherichia coli, Haemophilus influenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Proteus mirabilis, Serratia marcescens, Streptococcus pneumoniae, Chlamydia pneumoniae, Mycoplasma pneumoniae, Legionella pneumophilia, anaerobes bacteria, and influenza viruses. Atypical pathogens included C. pneumoniae, M. pneumoniae, and L. pneumophilia. CAP therapy was defined as β-lactams (ceftriaxone, ampicillin-sulbactam, amoxicillin-clavulanate, cefepime, ceftazidime, piperacillin-tazobactam) plus macrolide, or fluoroquinolones alone, and, eventually, in association with vancomycin, linezolid, or oseltamivir [5–7].

Definition of Immunocompromised and Study Groups ::: MATERIALS AND METHODS:
Immunocompromise was defined as the presence of ≥1 of the following risk factors: (1) AIDS, defined either as human immunodeficiency virus infection with CD4+ lymphocyte count <200/μL or by the occurrence of AIDS-defining conditions; (2) aplastic anemia; (3) asplenia; (4) hematological cancer, defined as lymphoma, acute or chronic leukemia, or multiple myeloma; (5) chemotherapy during the last 3 months; (6) neutropenia, defined as a neutrophil count <500/dL at complete blood cell count; (7) biological drug use (including trastuzumab and therapies for autoimmune diseases, eg, anti–tumor necrosis factor α, prescribed during ≥6 months before hospital admission); (8) lung transplantation; (9) chronic steroid use (>10 mg/d of prednisone or equivalent ≥3 months before hospital admission); (10) lung cancer with either neutropenia or chemotherapy; (11) other solid tumor with either neutropenia or chemotherapy; (12) other immunocompromise (any immunocompromised state, including congenital/genetic immunocompromise and immunosuppressive therapy due to hematological cancer/solid organ transplantation other than lung). Two study groups were identified: those with versus those without 1 risk factor for immunocompromise.

Statistical Analysis ::: MATERIALS AND METHODS:
Categorical variables, expressed as counts (percentages), were compared using the $\chi 2$ test. Continuous variables were compared using the unpaired Student t test or the Mann-Whitney test, when appropriate. Statistical significance was defined as $P < .05$. A network analysis was conducted to represent the frequencies of all immunocompromise variables and their relationships. The size of the circles (the circles visible in Figure 4 [network analysis], each representing a single risk factor for immunocompromise) represents both prevalence of the risk factor and strength of association with other variables.
The predictive value of each variable was categorized by quartiles and analyzed using a univariate regression logistic analysis. A multivariable model was obtained using a Cox regression analysis to identify independent predictors of specific pathogens, using an entry level of P value ≤0.05 and a removal level of P value ≥0.10. Hazard ratios and adjusted analyses were obtained. All statistical analyses were performed with IBM SPSS software (version 22, Statistics for Mac; version 22.0, IBM Crop), and Stata 13 software (StataCorp).

Prevalence of Risk Factors for Immunocompromise ::: RESULTS:
Among 3702 patients enrolled in the GLIMP database, ≥1 risk factor for immunocompromise was identified in 652 (17.6%). The prevalences of patients with pneumonia coming from the community and with ≥1 risk factor for immunocompromise differed among continents and countries, as depicted in Figure 1 and Supplementary Tables 1 and 2. The prevalence of immunocompromise was significantly higher in both North and South America than in the rest of the world (24.0% vs 16.5 [$P < .001$] and 24.8% vs 17.2 [$P = .006$], respectively) (Supplementary Table 1).

The prevalence of each risk factor for immunocompromise is depicted in Figure 2, with chronic steroid use (45.0%), hematological cancer (25.0%), and chemotherapy (22.0%) being the most frequent ones. A total of 312 patients (8.4%) had >1 risk factor for immunocompromise (Figure 3).

Network Analysis Among Risk Factors for Immunocompromise ::: RESULTS:
The results of the network analysis of all risk factors for immunocompromise are depicted in Figure 4. Relationships were identified between chemotherapy and solid tumor other than lung cancer, hematological cancer, and chronic steroid use, and between other immunocompromise and chronic steroid use.

Clinical and Microbiological Characteristics of Patients With Immunocompromise ::: RESULTS:
Clinical features and disease severity of immunocompetent versus immunocompromised patients are shown in Table 1 and Supplementary Table 3. Immunocompromised patients were significantly younger and malnourished, had a higher frequency of comorbid conditions, previous infections, and colonization by resistant pathogens, and had more frequent contacts with the healthcare system. The prevalences of severe pneumonia did not differ among the 2 study groups. Microbiological testing was performed in 91.0% (596 of 652) of immunocompromised and 86.0% (2626 of 3050) of immunocompetent patients (P < .001). Bacteremia was found in 6.0% (36 of 596) of immunocompromised and 5.5% (145 of 2626; P = .62) of immunocompetent patients. At least 1 positive culture was obtained in 40.0% (238 of 596) immunocompromised and 36.0% (935 of 2626) immunocompetent patients (P = .047). Microbiological findings are provided in Table 2 and Supplementary Table 4. Among pathogens covered by standard therapy, P. aeruginosa was more prevalent in immunocompromised patients (35 [5.9%] vs 98 [3.7%] patients; P < .02). Among pathogens not usually covered by standard therapy, immunocompromised patients were more likely to be infected by Nocardia spp. (4 [0.7%] vs 0 [0%] patients; P < .001), nontuberculous mycobacteria (NTM) (5 [0.8%] vs 2 [0.1%]; P < .002), A. fumigatus (8 [1.3%] vs 10 [0.4%]; P < .01), P. jirovecii (12 [2.0%] vs 5 [0.2%]; P < .02), and viruses, such as coronavirus (3 [0.5%] vs 3 [0.1%]; P < .047), and respiratory syncytial virus (6 [1.0%] vs 7 [0.3%]; P < .03). Once adjusted for confounders, no risk factors of immunocompromise have been recognized for P. aeruginosa infection. Likewise, pathogens not covered by usual CAP therapy were found to be associated not with immunocompromise but with chronic obstructive pulmonary disease (odds ratio [OR], 1.78; 95% confidence interval [CI], 1.07–2.99; P = .03), tracheostomy (2.91; 1.01–8.38; P = .048), and severe pneumonia (2.36; 1.42–3.93; P = .001) (Table 3).
Results showed that AIDS (OR, 15.10; 95% CI, 6.36–35.88; P ≤ .001) and hematological cancer (4.65; 91.85–11.69; P = .001) were independently associated with fungal infections; hematological cancer (5.49; 2.20–13.70; P < .001) and severe pneumonia (2.56; 1.27–5.19; P = .009) with infection by viruses other than influenza; and AIDS (4.41; 1.53–12.73; P = .006) and malnutrition (4.50; 2.08–9.72; P < .001) with mycobacterial infections. An additional analysis was conducted on mycobacteria, including M. tuberculosis and NTM. At multivariable analysis, M. tuberculosis was independently associated with malnutrition only (OR, 5.14; 95% CI, 2.21–11.93; P < .001). At univariate analysis, patients with AIDS were at higher risk for NTM (23.06; 4.39–121.12; P < .001). A subanalysis was conducted among patients with chronic steroid use versus other risk factors for immunocompromise. Patients with chronic steroid use seemed to be more frequently affected by bacteria not covered by standard CAP therapy (10 [3.4%] vs 1 [0.3%] patients; P = .002), Nocardia spp. in particular (4 [0.4%] vs 0 [0.0%]; P = .03). No differences in the severity of the disease were found (see Supplementary Table 5).

DISCUSSION:
The main findings of the present study are as follows: (1) 17.6% of patients admitted with pneumonia from the community have ≥1 risk factor for immunocompromise, with significant differences among continents and countries (ranging from 15.4% to 24.8% by continent and from 80.0% to 4.1% by country); (2) chronic steroid use is by far the most prevalent risk factor leading to immunocompromise, followed by hematological cancer and chemotherapy; (3) 1 of 2 immunocompromised patients has an overlap of ≥2 risk factors, which are also associated between one another in different ways; and (4) the 2 risk factors for immunocompromise independently associated with specific pathogens are AIDS (ie, fungal and mycobacterial infections) and hematological cancer (ie, fungal infection and viral infections other than influenza). Almost 1 in 5 hospitalized patients with CAP are not immunocompetent. Therefore, it is mandatory to provide clinicians with recommendations or guidelines for the management of hospitalized patients with pneumonia coming from the community who have risk factors for

immunocompromise. Currently, there are no guidelines for assessing pneumonia in immunocompromised patients coming from the community. Randomized controlled trials (RCTs) and observational prospective studies are missing owing to the fact that, generally, studies assessing management strategies for pneumonia exclude immunocompromised patients or take into account only a single specific risk factor [12–21]. This lack of information about immunocompromise could lead to both underestimation of the real prevalence with a higher rate of treatment failure and to overestimation and overuse of wide-spectrum antibiotics.

We found a 17.6% global prevalence of immunocompromise among patients coming from the community with pneumonia, with a significantly higher frequency in South and North America. This variability among continents and countries is probably attributable to different healthcare systems and rates of hospitalization of immunocompromised patients. Our analysis showed that the most frequent risk factor for immunocompromise is the chronic use of systemic steroids. Aging of the population and therapeutic advancements have favored the increased burden of chronic diseases and long-term therapies with immunosuppressive agents [8, 9]. In particular, steroids are the agents most frequently prescribed, for their wide spectrum of efficacy in several diseases [13, 17, 19]. Therefore, many patients presenting to the emergency room with pneumonia are receiving chronic steroid treatment. No data are available on this population group, and further studies are needed to characterize these patients and provide individualized management.

Hematological cancer and chemotherapy were other leading immunocompromised factors. These findings are consistent with those in previous studies; patients recruited in observational studies include patients with solid or hematological cancer and those who underwent chemotherapy with associated neutropenia [15–20, 22]. Dedicated guidelines and recommendations are available, especially on respiratory viruses, fungi, and P. jirovecii [23–26].

Our network analysis showed that several risk factors for immunocompromise show associations, especially chemotherapy, associated with hematological cancer and solid tumor, and other immunocompromise, associated with chronic steroid use. Moreover, neutropenic patients are well represented and mainly affected also by hematological cancer or under treatment with chemotherapy. Our results suggest that patients may have >1 risk factor characteristic and clinical assessment should be comprehensive, taking into consideration risk factors for immunocompromise and their associated biological mechanisms. In contrast, AIDS, lung transplantation, asplenia, and aplastic anemia seem to be less frequent at admission and to represent distinct clinical entities. Findings of previous studies seem to be in line with our results, with AIDS patients considered as a distinct patient population and with very few observational studies available on asplenia and aplastic anemia [21, 27–31]

In agreement with previous reports, S. pneumoniae is the leading microorganism in both immunocompromised and immunocompetent groups [32, 33]. Among pathogens covered by standard CAP therapy, only P. aeruginosa was more frequently isolated in immunocompromised compared with immunocompetent patients. These findings differ from microbiological results of previous studies. Gram-positive bacteria, especially S. aureus, were more frequently identified in patients with immunocompromise of different causes [22, 30, 34]. Only Li and coauthors [13] found patients with immunological disorders, treated with systemic steroids and cytotoxic agents, to have a higher incidence of infections caused by gram-negative bacteria, mainly P. aeruginosa. This similarity with our findings could be explained by the prevalence of patients exposed to chronic steroids in our cohort.

Among pathogens not covered by standard CAP therapy, immunocompromised patients were more frequently infected by Nocardia spp., NTM, P. jirovecii, A. fumigatus, and viruses other than influenza. Infections by P. jirovecii and NTM are frequently identified in patients with AIDS [35]. P. jirovecii is also frequent in other types of immunocompromise, such as solid or hematological cancer in patients who underwent chemotherapy [18, 19, 36]. Fungal infections (eg, Candida spp. and A. fumigatus) are highly incident in neutropenic hematological cancer patients [22, 37]. Viral infections other than influenza, especially respiratory syncytial virus, are more frequent in patients who underwent hematopoietic stem cell or lung transplantation [38, 39]. Conversely, Nocardia spp. infections are mainly described in solid organ transplant recipients [40]. These results, consistent with previous findings, suggest the need for a more in-depth microbiological workup, including community-acquired pathogens and microorganisms not covered by standard therapy. Surprisingly, we found that risk factors for immunocompromise were not independently associated with P. aeruginosa or non–community-acquired bacteria; in contrast, AIDS and hematological cancer are both associated with fungal, mycobacterial, and noninfluenza viral pneumonia, respectively. Empirical therapy should include P. aeruginosa coverage, which is highly

prevalent in immunocompromised patients. On the contrary, particular attention should be given to fungal, mycobacterial, and viral causes should be for patients admitted with AIDS and hematological cancer [21–29].

Finally, bacteremia rates did not differ between study groups. To our knowledge, there are no studies on bacteremia and immunocompromise in general. The majority of studies have focused on bacteremia in hematopoietic stem cell transplantation, with prevalences varying from 6% to 44% depending on the type of bacteria and host-related factors [41–43]. Few studies addressed this topic in kidney transplant recipients, reporting a prevalence of bacteremia ranging from 25% to 69% [44, 45]. Finally, few studies have addressed HIV and bacteremia, with prevalences ranging from 10% to 25%, depending on the pathogen and grade of immunosuppression [46, 47]. The prevalence of bacteremia in our study was 5T–6% in both immunocompetent and immunocompromised patients. Differences in the prevalence of bacteremia are due mainly to differences between the risk factors for immunocompromise in our study (chronic steroid use, hematological cancer, and chemotherapy) and those previously reported in the literature.

The current study has both limitations and strengths. First of all, to our knowledge, this is the first study showing a worldwide perspective on immunocompromise among patients coming from the community with pneumonia, with a large and diverse sample of patients enrolled across different countries in 6 continents. However, we were not able to involve many investigators from Asia and Africa, and most cases occurred in North America and Europe, thus limiting the generalizability of our findings. Another major limitation is the unfeasibility of grading the severity of immunocompromise and, therefore, stratifying patients and defining the physiopathological interaction between different risk factors, especially with regard to the use of biological drugs and chronic steroids. Furthermore, potentially important risk factors for an immunocompromised state, such as solid organ transplants other than lung, have not been specifically investigated. Finally, no outcome data have been collected, and this strongly limits our speculations as to the correct empiric antibiotic therapy for use in immunocompromised patients with CAP.

In conclusion, our study offers to the scientific community a perspective on immunocompromised patients coming from the community with pneumonia. Future prospective studies on patients with specific risk factors for immunocompromise could provide practical recommendations. In particular, it will be crucial to prepare guidelines on certain prevalent population groups, such as patients exposed to chronic steroids and those with hematological cancer.