Clinical Infectious Diseases

MAJOR ARTICLE

Prevalence and Etiology of Community-acquired Pneumonia in Immunocompromised Patients

Marta Francesca Di Pasquale,[1] Giovanni Sotgiu,[2] Andrea Gramegna,[1] Dejan Radovanovic,[3] Silvia Terraneo,[4] Luis F. Reyes,[5] Jan Rupp,[6] Juan González del Castillo,[7,8] Francesco Blasi,[1] Stefano Aliberti,[1] and Marcos I. Restrepo[9]; on behalf of GLIMP Investigators

[1]Department of Pathophysiology and Transplantation, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Internal Medicine Department, Respiratory Unit and Adult Cystic Fibrosis Center, University of Milan, [2]Clinical Epidemiology and Medical Statistics Unit, Department of Medical, Surgical and Experimental Sciences, University of Sassari, [3]Department of Biomedical and Clinical Sciences (DIBIC), University of Milan, Pulmonary Unit, Ospedale L. Sacco, ASST Fatebenfratelli-Sacco, and [4]Respiratory Unit, San Paolo Hospital, Department of Medical Sciences, University of Milan, Italy; [5]Microbiology Department, Universidad de La Sabana, Chia, Colombia; [6]Department of Infectious Diseases and Microbiology, University Hospital Schleswig-Holstein/Campus Lübeck, Germany; [7]Emergency Department, Hospital Clínico San Carlos, Universidad Complutense, and [8]Instituto de Investigación Sanitaria del Hospital Clínico San Carlos, IdISSC, Madrid, Spain; and [9]Division of Pulmonary Diseases and Critical Care Medicine, The University of Texas Health Science Center at San Antonio

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.

Keywords. pneumonia; multidrug-resistant pathogens; microbiology; MRSA; immunocompromise.

During initial evaluation of a patient coming from the community with pneumonia, the identification of possible risk factors for multidrug-resistant organisms or unusual pathogens is crucial [1–3]. Because a microbiological identification is found in about 30% of hospitalized patients with pneumonia coming from the community, and usually requires 24–48 hours to be available, most of patients are treated empirically [4]. Delay in initiation of appropriate empiric antibiotic therapy is a known risk factor for worse clinical outcomes [5–7]; therefore, it is relevant to promptly recognize patients at risk for specific pathogens, specially multidrug-resistant or atypical microbes [1–3].

The aging of the population and advancements in therapeutic protocols have led to an increase prevalence of chronic diseases as well as long-term treatments with immunosuppressive agents [8, 9]. Thus, among patients with pneumonia coming from the community and admitted to the hospital, the number who might not be fully immunocompetent is constantly increasing [8, 9]. Nevertheless, the real prevalence of immunocompromise among patients with pneumonia coming from the community is still unknown. Moreover, guidelines for community-acquired and hospital-acquired pneumonia did not address this topic—what is more, they specifically excluded patients with clinical characteristics determining immunocompromise [5–7], and current evidence in literature is also scarce.

To our knowledge, there are no studies addressing the clinical evaluation and initial empirical antibiotic coverage of patients coming from the community with pneumonia and immunocompromise. Moreover, specific risk factors to assess the causative microbiology and help clinicians choose more appropriate management for these patients have not been clearly identified. Thus, the aim of the current study was to identify the prevalence,

Received 24 May 2018; editorial decision 3 August 2018; accepted 20 August 2018; published online August 23, 2018.

Correspondence: S. Aliberti, Department of Pathophysiology and Transplantation, University of Milan, Internal Medicine Department, Respiratory Unit and Cystic Fibrosis Adult Center, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Francesco Sforza 35, 20122 Milan, Italy (stefano.aliberti@unimi.it).

Clinical Infectious Diseases® 2019;68(9):1482–93

DOI: 10.1093/cid/ciy723

type, microbiology, and intercorrelations between different risk factors for immunocompromise in hospitalized patients with pneumonia coming from the community.

MATERIALS AND METHODS

Study Design and Population

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

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

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

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

Categorical variables, expressed as counts (percentages), were compared using the χ^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).

RESULTS

Prevalence of Risk Factors for Immunocompromise

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).

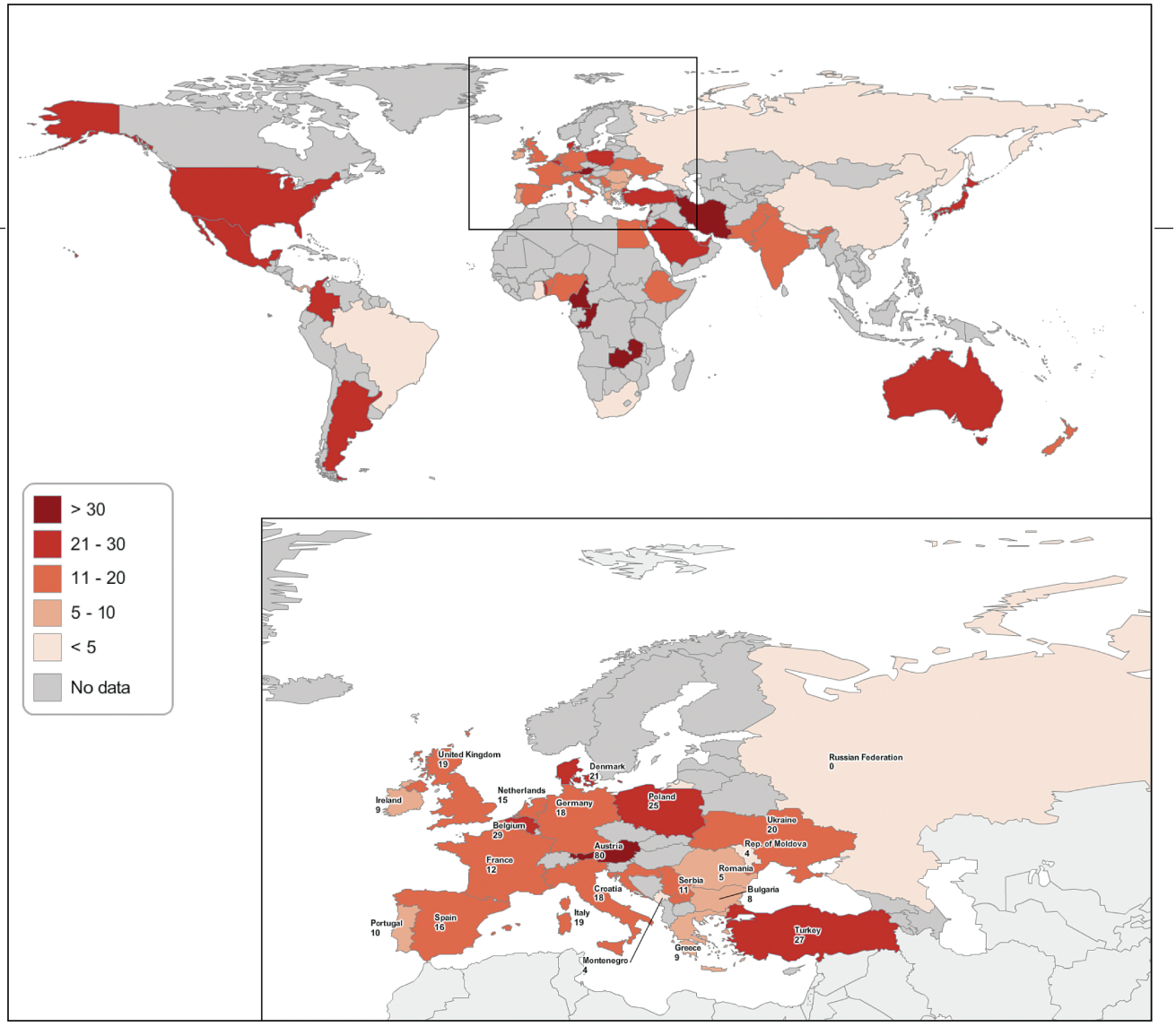

Figure 1. Distribution of prevalence of immunocompromise among the different countries participating in the study, categorized as no data, <5%, 5%–10%, 11%–20%, 21%–30%, or >30% of total cases.

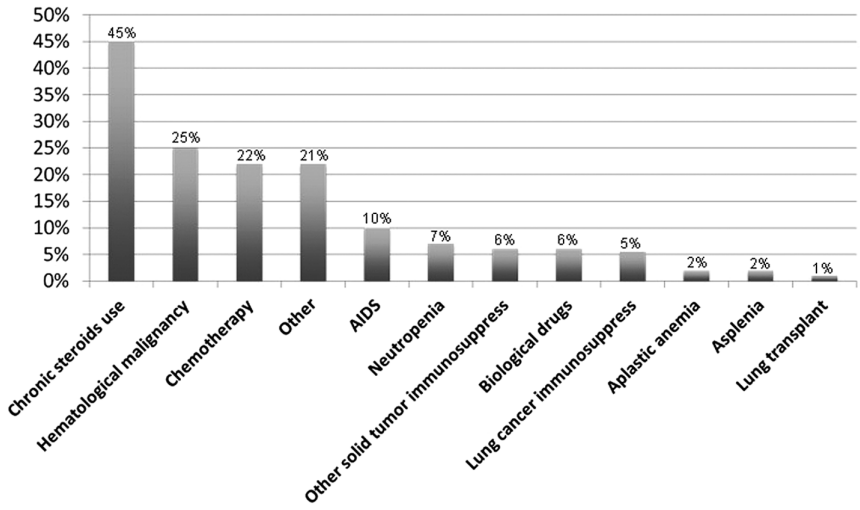

Figure 2. Prevalence of each single risk factor for immunocompromise.

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

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

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%]

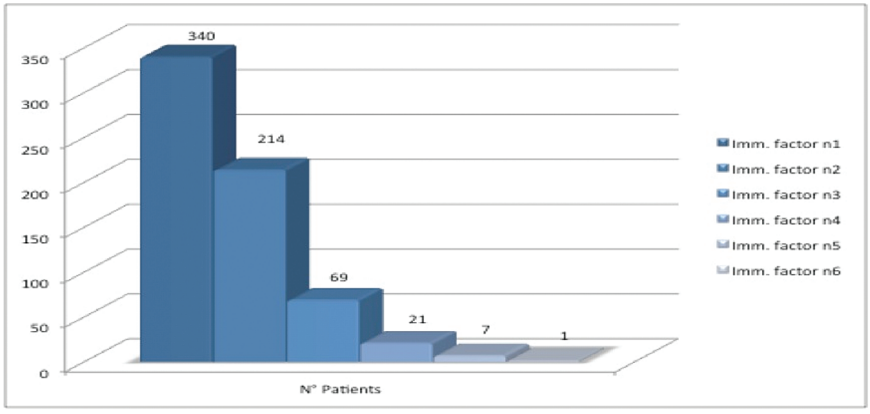

Figure 3. Prevalence of the number of risk factors present simultaneously in a single patient.