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Microbiological ascertainment in patients with pneumonia: the experience of a teaching hospital in Rome

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Abstract

Objectives. Pneumonia still remains a problem from the clinical and public health viewpoint because of the relevant epidemiological burden. The etiological diagnosis is important in the light of avoiding unnecessary antibiotic treatment and choosing the most appropriate therapeutical approach. This study is aimed at providing evidence on the proportion of microbiological ascertainment in pneumonia-related hospitalizations in one of the most important teaching hospitals in Rome.

Methods. The study relied on the record linkage of two administrative databases of the same hospital: the electronic hospital discharge register and the microbiology laboratory surveillance database.

Results. 2819 records were identified, where 46% had a microbiological ascertainment, significantly higher in males than in females (51% *vs* 40%) and in cases of pneumonia reported in secondary diagnosis instead of primary diagnosis (52% *vs* 42%). Medical patients had significantly lower proportion of ascertainment compared to surgical patients (43% *vs* 67%) whereas there were not differences between patients with emergency and elective admission. The overall mortality was 17%. Mortality was significantly higher: in surgical compared to medical patients (27% *vs* 15%), in ventilated compared to not ventilated patients (41% *vs* 11%), in cases with secondary diagnosis of pneumonia compared to a primary diagnosis (23% *vs* 11%) and in hospitalized in intensive care unit-ICU- rather than in non-ICU (71% *vs* 12%).

Conclusion. The proportion of microbiological ascertaiment in pneumonia remains less than 50%. Albeit in line with other evidence, this result should call the attention on the impact of unknown etiological diagnosis on antibiotic treatment and resistance.

Key words
- pneumonia
- etiology
- microbiological ascertainment
- diagnosis

INTRODUCTION

Pneumonia is a leading cause of morbidity and mortality in adults [1-2] with a major epidemiological relevance worldwide. In fact, the evidence reports that lower respiratory tract infections (LTRI), including pneumonia, are the fourth most common cause of death with

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1.9 million people over 14 years of age dying every year [3]. Furthermore, they are responsible for more disability-adjusted life years lost around the world than any other category of disease, including cancer and cardiovascular diseases [4]. In Europe, the cost of caring for patients with pneumonia is estimated to be around € 10.1 billion annually [5]. Pneumonia represent 9.4% of severe infections [6] with a reported incidence varying considerably among countries (1.7-11.6/1000 person-years) [7-9] and increasing with age (7.65-15.3/1000 person-years in adults aged ≥ 65 years) [1-13]. Albeit pneumonia can affect anyone, it occurs especially with increasing frequency in individuals whose immune system is deficient or compromised [14]. Also, infants and very young children are highly vulnerable, as well as the elderly. In fact, at both extremes of age, the increased risk relates in part to impaired immunity and often determines hospitalization [15]. Some studies have demonstrated an increasing trend towards hospitalization, in particular in the elderly [16-18]. In the USA individuals older than 65 years of age account for almost two thirds of hospitalizations and 90% of deaths from pneumonia [16]. Because of population ageing and the growing number of patients with multiple vulnerabilities, beside the increased proportion of cases requiring hospitalization, there has been also a growth in the proportion of patients experiencing poor outcomes [19]. Antimicrobial resistance may contribute to poor outcomes and is linked to inappropriate use of antibiotics. Thus, information on the potential pathogens is important for a proper antimicrobial treatment, avoids inappropriate antibiotics prescriptions and eventually, the antimicrobial resistance [20-22]. Furthermore, the identification of the pathogens is a key factor for a good prognosis, especially in cases with mixed etiology, who often develop severe pneumonia, and have longer hospitalization and poorer outcomes [23-25].

Although clinical variables are independently associated with the detection of a pathogen group, there are no reliable clinical predictors to distinguish causative aetiologies [25]. Therefore, diagnostic testing, with the ability to detect the causative pathogens have the potential to guide to a more rational use of antibiotics, firstly by distinguishing between viral and bacterial infections, and then by identifying specific pathogens and their antibiotic resistance pattern. Patients gain more from a rapid and effective use of antibiotics and society gains from the reduction of the unselective use of antibiotics, that has been considered as a major factor driving the emergence and spread of resistance.

In the past 20 years, there has been a decline in interest and perceived need for microbiological analysis in pneumonia, to the point that the vast majority of patients have no microbial pathogen diagnosis [26].

Moreover, it should be noted that in many patients the etiology remains unknown even after routine diagnostic workup. The etiology of pneumonia has still not been well characterized [27] and remains unknown nearly in 50% of cases [28]. The lack of information may be due to a range of common clinical scenarios depending on the severity of infection, the potential consequences of an incorrect diagnosis, timescales in which diagnostic information is required, clinical setting and clinicians'decision making.

This study aimed at providing evidence about the proportion of microbiological ascertainment of pneumonia in a big teaching hospital in Italy and at elucidating characteristics associated with the request of microbiological ascertainment and its impact on mortality.

METHODS

A retrospective cohort study has been performed at the "A. Gemelli" Teaching Hospital including all discharged patients from November 13th 2010 to March 26th 2013 with a diagnosis of pneumonia. For the purpose of this study the term "Pneumonia" was referred to pneumonia from any cause. Pneumonia related hospitalizations were assessed on the basis of the International Classification of Diseases, 9th revision – Clinical Modification (ICD-9-CM) codes [29] using the electronic hospital discharge register. All patients' records reporting a first-listed ICD-9-CM code discharge diagnosis of pneumonia (003.22, 011.6, 052.1, 055.1, 073.0, 115.05, 115.15, 115.95, 130.4, 480-487.0, 495.7, 495.9, 506.0, 507, 517.1, 770.0) were considered. Similarly, a first-listed discharge diagnosis of meningitis or septicemia (003.21, 013.0, 036.0, 036.1, 047, 049.0, 049.1, 053.0, 054.72, 072.1, 090.42, 091.81, 094.2, 098.82, 100.81, 112.83, 114.2, 115.01, 115.11, 115.91, 130.0, 320, 321, 322, 003.1, 020.2, 022.3, 031.2, 036.2, 036.3, 038, 054.5, 785.50, 785.59, 790.7, 790.8) in addition to a diagnosis of pneumonia in another diagnostic field was considered to identify the study population. Microbiological tests performed in the same time period on respiratory tract (e.g., sputum) and blood cultures, as well as urine tests for Streptococcus pneumonia and Legionella pneumophila antigens were collected from the Institute of Microbiology of the "A. Gemelli" Teaching Hospital. Electronic hospital discharge records were used to collect data on patients' demographic characteristics and hospitalization information. As for patients' characteristics the following information was recorded: date of birth, age, sex, health status at discharge (dead or not). Comorbidity was also assessed using ICD-9-CM codes and Charlson's index syntax integrated to Stata [30]. The Charlson Comorbidity Index (CCI) is a method of categorizing comorbidities of patients based on the ICD-9-CM codes. Each comorbidity category has an associated weight (from 1 to 6), based on the adjusted risk of mortality or resource use, and the sum of all the weights results in a single comorbidity score for a patient. A score of zero indicates that no comorbidities were found. A score equal to one represents the presence of one of the following diseases: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, rheumatoid disease, peptic ulcer disease, mild liver disease and diabetes. In contrast, a score of 2 indicates the presence of more serious comorbidities such as complicated diabetes, hemiplegia or paraplegia, renal disease, cancer, moderate / severe liver disease, metastatic cancer and AIDS or the presence of more than one comorbidity.

Patients with weakened immune system were identi-

fied according to the following codes: V58.12, 283.10, 287.31, 283.0, 279.3, ,279.2, 279.06, 279.03, 203.80, V08, 079.53, 042.

With respect to organizational features, the following variables were extracted: type of discharge, hospital ward, length of stay (LOS), modality of admission, diagnosis, Diagnosis Related Group (DRG), type of DRG. Hospital wards were distinguished in intensive care unit (ICU) and non-ICU. Ventilation was assessed according to the following procedure codes: 96.04, 96.7, 96.71, 96.72, 93.9. For patients with multiple eligible admissions in the study period, each hospitalization was considered as an independent observation except for re-admissions until 30 days that were excluded because possibly related to the first admission.

Data from the electronic hospital discharge register and from the microbiology laboratory database were merged by means of the unique identity number which is automatically assigned to each patient once admitted to the "A. Gemelli" Teaching Hospital and used during all hospitalizations or services provided by the hospital. Data from the microbiology laboratory database were considered only if the microbiological ascertainment was requested during the hospital stay. The deterministic record linkage allowed calculating the total number of microbiological ascertainments for each patient during the hospitalization, and assessing their positive and negative results. With this respect, microbiological ascertainment was defined as "positive" if the patient had at least one positive finding. The proportion of ascertainment was yielded with 95% Confidence Interval. Differences between groups (patients with and without microbiological ascertainment request; patients died or alive at discharge) have been analyzed through the application of Chi-squared test with continuity correction for categorical variables and non parametric tests for continuous variables. All the significant variables, and the ones with $0.05 < p < 0.25$ detected in the univariate analysis, were included in a multiple regression analysis. The analysis was performed with a logistic binomil-regression model having death as outcome and the level of statistical significance was set at 0.05. Stata 12 software was used for the deterministic record linkage and the statistical analysis.

RESULTS

A total of 2819 records were included in the present study; 1225 (43.46%) referred to females; patients' median age was 71.3 years (interquantile range, 52.4 to 82.1). 1705 records (60.48%) were referred to people over 64 years old. 50.16% of patients had comorbidities, like cerebrovascular disease, congestive heart failure, acute myocardial infarction, renal diseases, chronic obstructive pulmonary disease, with a predominance of cancer (12.98%). 1597 records (56.65%) had pneumonia reported in primary diagnosis and 365 (12.95%) had a surgical DRG type. Among all patients only 229 (8.12%) required intensive care. The median LOS was 12 days (interquantile range, 7 to 19). The characteristics of the study sample are presented in *Table 1*.

A microbiological ascertainment was requested in 1303 (46.22%) patients but only 743 (57.02%) yielded a positive result. Blood culture was the most common requested ascertainment (31.1%) with a positivity finding in 25.17% of cases *(Table 2)*. Naso-faringeal swabs were obtained from 54 (1.92%) patients, a sputum specimen from 479 (16.99%), a bronchial washing from 390 (13.83%), a bronchial aspirate from 65 (2.31%), a pleural fluid specimen from 53 (1.88%). Eventually, urine specimen was obtained from 629 (22.31%) and the request of Legionella and streptococcal antigen were performed in 22.31% and 9.01% respectively. Diagnostic results were available from 743 individuals. We identified 80 different

Table 1
Characteristics of the study sample

	N (%)
Diagnosis of pneumonia	
Primary	1597 (56.65)
Secondary	1222 (43.35)
Age (2802)*	71.3 [52.4-82.1]
Sex	
Females	1225 (43.46)
Males	1594 (56.54)
Modality of admission	
Emergency	611 (21.67)
Elective	2208 (78.33)
DRG Type	
Medical	2454 (87.05)
Surgical	365 (12.95)
Hospital ward	
Non – ICU	2590 (91.88)
ICU	229 (8.12)
Length of stay (days)*	12 [7-19]
Comorbidity	
Myocardial infarction	45 (1.60)
Congestive heart failure	250 (8.87)
Peripheral Vascular Disease	30 (1.06)
Cerebrovascular disease	276 (9.79)
Chronic Obstructive Pulmonary Disease	315 (11.17)
Rheumatoid Disease	6 (0.21)
PUD (Peptic Ulcer Disease)	6 (0.21)
HP/PAPL (Hemiplegia or Paraplegia)	17 (0.6)
RD (Renal Disease)	202 (7.17)
Cancer	366 (12.98)
Metastatic Cancer	102 (3.62)
AIDS	80 (2.84)
Dementia	43 (1.53)
Microbiological ascertainment	
Present	1303 (46.22)
Absent	1516 (53.78)

*median [interquartile range]

Table 2
Characteristics of collected specimen

		Rates		Positive specimen
Analyzed specimen	**N**	**% [95% CI]**	**N**	**% [95% CI]**
Blood culture	878	31.1 [29.44- 32.89]	221	25.17 [22.33-28.18]
Urine	629	22.3 [20.79- 23.9]	38	6.04 [4.31-8.20]
Sputum	479	17 [15.62- 18.43]	399	83.3 [79.65-86.53]
Bronchial washing	390	13.8 [12.58- 15.16]	304	77.95 [73.5-81.97]
Bronchial aspirate	65	2.3 [1.78- 2.93]	54	83.08 [71.73-91.24]
Pleural fluid	53	1.9 [1.41- 2.45]	12	22.64 [12.28-36.21]
Naso-faringeal swabs	54	1.9 [1.44- 2.49]	34	62.96 [48.74-75.71]
Biopsy material	4	0.1 [0.04- 0.36]	2	50 [6.76-93.24]

¥ -% in calculated considering N = 2819

types of etiologic agents causing pneumonia. The most common pathogen was *S. pneumoniae* identified in 299 (40.24%) patients *(Supplementary Table 1, available online)*.

Table 3 reports the results of the univariable analysis investigating the association between patients' and organizational characteristics and the request of the ascertainment. The latter was significantly lower in females as compared to males; in patients with a primary diagnosis of pneumonia in comparison to patients with a secondary diagnosis of pneumonia; in patients with grouped Charlson index equal to 0 or 1 as compared to 2 and in patients with a medical DRG. The median age of patients who had a microbiological ascertainment was significantly lower, 66.8 (interquantile range, 49.3 to 78.5) as compared to 74.7 (interquantile range, 57.3 to 84.3) for the ones who had not it and the proportion of ascertainment was significantly lower in the pediatric age compared to the other groups. More than half of the pediatric group and of elderly did not have a microbiological ascertainment. There were no significant differences between patients admitted from the emergency room and those with an elective admission. Among 543 patients who required ventilation, 355 (65.38%) had a microbiological ascertainment and 275 (77.46%) a positive result. 66 (66.67%) patients with compromised immunity (AIDS included) had a microbiological ascertainment but only in 44 (66.67%) the etiology was identified.

The total number of deaths was 467 (16.57%) across the 2819 records. Higher mortality was observed in people over 64 years of age, 22.2% (N = 379) as compared to 9% (N= 84) and 1.6% (N = 4) in people from 15 to 64 years old and younger than 15 years respectively. Several variables showed an association with mortality in the univariate analysis in *Table 4*. Mortality was significantly higher in patients with secondary diagnosis of pneumonia, hospitalized in ICU wards, with an elective admission and a surgical DRG. Mortality was also higher in people having a microbiological ascertainment. After fitting the model for the multiple regression analysis of mortality: age, sex, CCI, the microbiological ascertainment, type of admission, ventilation, hospital ward diagnosis of pneumonia (primary or secondary) and admission modality were considered. As shown in *Table 5* only five factors were eventually associated with mortality: age, elective admission, ventilation, secondary diagnosis of pneumonia and admission in ICU (all associated with increased mortality).

Table 3
Microbiological ascertainment proportion and the association with patients' and organizational characteristics

	Microbiological ascertainment		
	Yes N (%)	**No N (%)**	**p-value**
Sex			
Female	496 (40.49)	729 (59.51)	< 0.001
Male	807 (50.63)	787 (49.37)	
Age	66.8 [49.3-78.5]	74.7 [57.3-84.3]	< 0.001
Age groups			
< 15 years	87 (34.66)	164 (65.34)	< 0.001
15-64 years	529 (62.53)	317 (37.47)	
> 64 years	687 (40.29)	1018 (59.71)	
CCI			
0	634 (45.12)	771 (54.88)	< 0.001
1	236 (41.55)	332 (58.45)	
2	433 (51.18)	413 (48.82)	
Diagnosis of pneumonia			
Primary	672 (42.08)	925 (57.92)	< 0.001
Secondary	631 (51.64)	591 (48.24)	
DRG Type			
Surgical	244 (66.85)	121 (33.15)	< 0.001
Medical	1059 (43.15)	1395 (56.85)	
Hospital ward			
Non-ICU	1135 (43.82)	1455 (56.18)	< 0.001
ICU	168 (73.36)	61 (26.64)	
Admission Modality			
Emergency	299 (48.94)	312 (51.06)	0.128
Elective	1004 (45.47)	1204 (54.53)	

Table 4
Mortality association with patients' and organizational characteristics

	Dead		
	Yes N (%)	No N (%)	p-value
Sex			
Female	190 (15.51)	1035 (84.49)	0.186
Male	277 (17.38)	1317 (82.62)	
Age group			
< 15 years	4 (1.59)	247 (98.41)	< 0.001
15-64 years	84 (9.03)	846 (90.97)	
> 64 years	379 (22.23)	1326 (77.77)	
CCI			
0	203 (14.45)	1202 (85.55)	0.009
1	110 (19.37)	458 (80.63)	
2	154 (18.2)	692 (81.8)	
Microbiological ascertainment			
Not Present	216 (14.25)	1300 (85.75)	< 0.001
Present	251 (34.24)	482 (65.76)	
Age*	79.4 [69.6-87.1]	69.2 [49.2-80.6]	< 0.001
Length of stay	13 (5-23)	12 (7-9)	< 0.001
Diagnosis of pneumonia			
Primary	180 (11.27)	1417 (88.73)	< 0.001
Secondary	287 (23.49)	935 (76.51)	
DRG Type			
Surgical	100 (27.4)	265 (72.6)	< 0.001
Medical	367 (14.96)	2087 (85.04)	
Hospital ward			
Non-ICU	305 (11.78)	2285 (88.22)	< 0.001
ICU	162 (70.74)	67 (29.26)	
Admission Modality			
Emergency	72 (11.78)	539 (88.22)	< 0.001
Elective	395 (17.89)	1813 (82.11)	
Ventilation			
Yes	222 (40.88)	321 (59.12)	< 0.001
No	245 (10.76)	2031 (89.24)	

*median [interquartile range]

Table 5
Mortality multiple regression

Variables	OR	[95% CI]	p-value
Age	1.06	[1.05- 11.07]	< 0.001
stay in ICU *vs* non-ICU	16.34	[10.67- 25.01]	< 0.001
Ventilation	3.94	[2.91- 5.33]	< 0.001
Secondary (*vs* primary) diagnosis of pneumonia	1.84	[1.43- 2.37]	< 0.001
Surgical *vs* medical DRG	0.72	[0.49- 1.04]	0.077
Male *vs* female	1.16	[0.91- 1.49]	0.230
Presence of microbiological ascertainment	1.19	[0.92- 1.53]	0.178
Charlson index 1 (*vs* 0)	0.78	[0.58- 1.08]	0.137
Charlson index 2 (*vs* 0)	1.17	[0.88- 1.55]	0.274
Elective *vs* emergency admission	1.41	[1.01- 1.96]	0.041

DISCUSSION

This work pointed out that a microbiological ascertainment in patients with a diagnosis of pneumonia in a big teaching hospital in Rome was requested in less than 50%. Blood culture was the most common requested ascertainment and *S. pneumoniae* was the most common identified etiologic agent. If data about blood culture as the most common diagnostic test and *S. pneumoniae* as the most common pathogen may be confirmed by other multicentre and international evidence [31], the comment on the proportion of ascertainment is not straightforward. Some international studies performed on adult patients with community-acquired pneumonia (CAP) found that all or almost most of patients underwent a diagnostic test [31, 32], but other evidence suggested a lower proportion of etiological diagnosis [34]. This heterogeneity is actually expected because of discordant or not conclusive recommendations released by scientific societies. The guidelines on CAP yielded by the Infectious Disease Society of America/American Thoracic Society (IDSA/ATS) suggests a microbiology ascertainment in cases of severely ill patients (including those in ICU) or if a pathogen likely to change antibiotic management is suspected [1]. Similarly, as for children, the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America recommends to collect blood cultures in case of moderate or severe CAP even though the definition of the severity is not well established [35]. On the contrary, the ascertainment is suggested in case of Hospital-Acquired Pneumonia (HAP) or Ventilator-Associated Pneumonia (VAP) [36]. In this light, the elaboration on our results is complex due to the lack of differentiation between types of pneumonia. Nevertheless, looking at the percentages of people both admitted in ICU and with comorbidities – indeed most likely to have moderate to severe CAP – it can be assumed that the proportion of microbiological ascertainment shown in our study is acceptable considering current guidelines and the evidence that there is a worldwide tendency to over-testing considering IDSA/ATS guidelines [31].

Independently of the proportion of microbiological ascertainment, an etiological diagnosis was overall achieved in 26.4% of cases and this result is aligned with other evidence coming from adults but also elderly and children [31, 32, 37]. The positivity rate found in different specimens is in agreement with international literature and suggests that blood culture has low sensitivity in detecting pneumonia aetiology [31, 35].

The request of the ascertainment was significantly higher, with a proportion over 60%, in adults, in patients staying in ICU and in patients with a surgical DRG. Furthermore, it was higher in cases requiring

ventilation and with underlying immunocompromised conditions. These data seem to reflect the current recommendations on etiological diagnosis of pneumonia.

With respect to mortality, our overall results seem to be higher than those released by other studies such as the REACH [32], but it should be taken into consideration that our work encompassed all patients with a diagnosis of pneumonia independently by the fact that it was community or hospital acquired. Higher mortality was observed in people over 64 years of age, in patients with a secondary diagnosis of pneumonia, and in those hospitalized in ICU, with an elective admission and with a surgical DRG. These results may be related to the more severe clinical course in these categories of patients. Considering the high frequency of *S. pneumoniae* among the etiological agents, the pneumococcal vaccination of this group of patients could be widely worthwhile. In fact, elderly as well as people with comborbidities are considered as eligible candidates for pneumococcal vaccination and physicians may benefit from the hospital stay of these patients to raise their awareness on the need for vaccination [33]. A finding arising from univariable analysis that is worth discussing was that mortality was higher in people having a microbiological ascertainment. The evidence on this aspect is counteracting with data showing a reduced mortality in patients who underwent multiple guideline concordant microbiological testing for CAP [34] and evidence suggesting that microbiological diagnosis is associated to worse clinical course and higher in-hospital mortality rate [38]. This could be explained by the delay in the laboratory results and eventually in setting a specific therapy. In fact, the results of microbiological ascertainment may allow to change antibiotic treatment, but initial antibiotic treatment modification has been shown associated with higher resource use and costs as well as higher mortality [39]. This should call the attention on the importance of deepening the knowledge of the aetiology of pneumonia in order to better direct the empirical therapy [31] and to counter the problem of antibiotic resistance.

Our study has some limitations. The most important one is that we did not make any distinction among different types of pneumonia because the study was only relied on administrative data flows. This aspect could limit the interpretation and generalizability of results but, on the other hand, makes it possible to have a thorough overview of current practice with respect to all patients discharged with a diagnosis of pneumonia. Nevertheless, because of the source used to collect data, our study did not encompass other factors that have been shown important in the assessment of the proportion of ascertainment and pneumonia outcomes, such as the specimen quality, potential antimicrobial treatment before the hospital admission, possible change of the therapy after consulting the microbiological ascertainment result [40]. Another pitfall could raise from the potential inappropriate use of ICD-9-CM codes which could lead to misclassification. Nevertheless, in our opinion, this problem could mainly affect the identification of potential comorbidities instead of the selection of eligible study population. Another significant limitation is the lack of laboratory data regarding the viral specimen that could possibly increase the proportion of ascertainment.

Among the strengths of the study we should mention that many records were analysed and that selection bias can be ruled out because all records reporting the selected ICD-9-CM were considered. Furthermore, this study is one of the few attempts to describe the actual diagnostic management of pneumonia in the Italian hospital setting and to investigate how the latter relates with the outcome.

CONCLUSION

Hospital information data can be used to give a timely and inexpensive picture of several diseases that frequently require hospitalisation and are not included in special surveillance systems or more analytical registries. The population ageing will strongly increase the burden of pneumonia in the near future. Pathogen's detection in pneumonia is essential to inform clinical management decisions and research priorities especially in the fields of vaccine and antibacterial and antiviral development [41, 42].

Conflict of interest statement

There is no conflict of interest that could compromise the impartiality of the research reported.

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