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Letters to the Editor

A six-year microbiologic study of hospital-acquired and health-care associated parapneumonic pleural infection

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Hospital-acquired (HA) pleural infections, i.e. those with onset of over 48 h upon hospitalization, are associated with high rates of mortality [1]. Health-care associated (HCA) pleural infections are defined as those manifested at hospital admission or within 48 h of admission in patients complying with one of the following criteria: residence in a long-term-care facility, hospitalization within the last four weeks and receipt of intravenous medical therapy within the previous 30 days [2]. The microbiology of HA and HCA-pleural infections in Greece, has not been investigated so far and currently, empirical antimicrobial therapy is based on microbiological data available from other countries. We therefore aimed to identify and compare the microbiological profile (causative pathogen and drug-sensitivity) responsible for HA and HCA-pleural infections in Greece.

We conducted an observational study over a period of more than six years: 2012- December 2013, retrospectively and January 2014–May 2018, prospectively. Patients aged 18 years and above, with pleural fluid culture-positive HA or HCA pleural infections were included. Exclusion criteria were: community-acquired pleural infection, traumatic empyema, mycobacterial infections and infections caused by extra-thoracic sepsis. The retrospective cohort included patients from four and in prospective one, from six major Greek hospitals. Drug resistance data were derived from the prospective cohort. Multidrug resistance (MDR) was defined as resistance to at least one agent in three or more antimicrobial categories [3]. Specimens were cultured according to the usual laboratory routine. Identification and susceptibility testing were performed with VITEK 2 (Bio Merieux). These data were collected during a larger study that focuses on the microbiology and clinical features of culture-positive community acquired parapneumonic pleural infection (results pending).

A total of 123 patients with HA and HCA parapneumonic pleural infection were analyzed: 64 patients from the retrospective and 59 from the prospective group. In the retrospective group, 23 patients had HA-pleural infection, 16 had HCA-pleural infection and 25 patients could not be classified to a subgroup due to incomplete data from medical history and were excluded from further analysis. In the prospective group, 16 patients suffered from HA-pleural infection and 43 from HCA-one.

The overall microbiological profile is presented in Table 1. Among all isolates, the most common pathogens were gram-negative bacteria (52.6%), followed by gram-positive cocci (35.6%), anaerobes (6.8%) and fungi (5%). The most frequently identified pathogen was *Klebsiella* spp. HA-infections were more commonly caused by gram-negative microbes (75%). *Klebsiella spp* (22.5%) and *Acinetobacter spp* (20%) were the major causes of HA-infections. The most common pathogens identified among HCA-patients were gram-positive cocci (43.6%), followed by gram-negative bacteria (41%), anaerobes (9%) and fungi (6.4%). *Streptococcus spp group* (19.2%) and *enterococcus spp* (10.3%) prevailed among Gram-positive, while the most common Gram-negative pathogens were *pseudomonas spp* (11.5%) and *klebsiella spp* (10.3%).

Overall MDR was found in 13/40 (32.5%) HA-related strains and in 17/78 (21.8%) HCA- related ones. Notably, in HA-patients, MDR strains were found in 100% of *Staphylococcus aureus, Klebsiella spp, Enterococcus spp, Pseudomonas spp, Acinetobacter* spp. However, in HCA-patients the MDR rates were lower, i.e. *Staphylococcus aureus* 50%, *Klebsiella spp* 60%, *enterococcus spp* 34%, *Pseudomonas spp* 50% and *Acinetobacter spp* 67%. The difference in MDR rates of each pathogen category was not statistically significant ($p > 0.05$) between HA- and HCA-patients, more likely due to the limited sample size.

In this study, we observed that the main causative agents of HA-pleural infections are the gram-negative bacteria, mainly, *klebsiella* spp. This comes in accordance with previous studies from the USA and Taiwan [4,5] but not with this from Australia in which the main cause was *s.aureus* [6]. Second, it is important to note that in HCA-infections, the most common pathogens were *enterococcus spp* and *other streptococci*. Another study from Japan describes *streptococcus species* as the leading cause of HCA-pleural infections [1].

No differences were found between our HA-group (2.5%) and this from Australia (2.5%) in the anaerobic pleural infections [6]. As far as our HCA-group is concerned, the rate was higher (9%) compared to HA-one (2.5%) ($p > 0.05$), in contrast with the study of Japan in which anaerobic organisms grew in 23% of HA-cases and in 17% of HCA-ones [1]. This might be possible attributed to different underlying health problems between patients of the different cohorts.

Moreover, it is noteworthy the increased incidence of fungal infections in patients with HCA-pleural infection (6.4%) compared to HA-ones (2.5%) possibly suggesting compromised immunity [7].

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Table 1
Microbiology of hospital acquired (HA) and health care associated (HCA) pleural infections. Multiple isolates (≥2) were observed in 2 patients with HA-pleural infection (5.3%) and in 13 with HCA-one (21.7%).

Pathogen	Patients with positive pleural fluid culture [number (%)]	
	HA-infections	HCA-infections
Gram(+)	8 (20)	34 (43.6)
S.anginosus group	1 (2.5)	5 (6.4)
S.mitis group	1 (2.5)	3 (3.8)
S.pneumoniae	0 (0)	1 (1.3)
Other s.viridans	1 (2.5)	5 (6.4)
S.agalactiae	0 (0)	1 (1.3)
Enterococcus spp	2 (5)	8 (10.3)
S.aureus	3 (7.5)	6 (7.7)
Other staphylococci	0 (0)	3 (3.8)
Actinomyces	0 (0)	2 (2.6)
Gram(−)	30 (75)	32 (41)
Klebsiella spp	9 (22.5)	8 (10.3)
Acinetobacter spp	8 (20)	5 (6.4)
Pseudomonas spp	5 (12.5)	9 (11.5)
Providencia stuartii	3 (7.5)	2 (2.6)
Escherichia coli	1 (2.5)	3 (3.8)
Proteus mirabilis	0 (0)	1 (1.3)
Stenotrophomonas spp	1 (2.5)	1 (1.3)
Other	3 (7.5)	3 (3.8)
Anaerobes	1 (2.5)	7 (9)
Prevotella spp	0 (0)	3 (3.8)
Fusobacterium spp	0 (0)	1 (1.3)
Clostridium spp	1 (2.5)	2 (2.6)
Bacteroides spp	0 (0)	1 (1.3)
Fungi	1 (2.5)	5 (6.4)
Candida spp	1 (2.5)	4 (5.1)
Aspergillus fumigatus	0 (0)	1 (1.3)

Interestingly, we herein show that multi-drug resistant microbes such as Extended Spectrum B-Lactamase-producing Klebsiella (ESBL), Vancomycin-resistant enterococci (VRE), fungi, *Acinetobacter spp* and *Pseudomonas spp*, were isolated from HA and HCA-pleural fluid. This observation agrees with the study from Japan and could be explained by the high number of interventions (i.e. catheters) in these patients or by their immunosuppression [8].

This study has some limitations. First, a significant part of our cohort was investigated retrospectively. Relative to this, although 25 patients from the retrospective part had characteristics of HCA-pleural infection, they were not included due to the fact that the time of initiation of the infection was unclear. On the other hand, we have also accomplished a 4-year multi-center, prospective part, determining the complete drug sensitivity profiles of all isolates. Second, patients, with pleural infection and pathogens isolated only from the blood or sputum were not included in our analysis, since we recruited patients with positive pleural fluid, aiming at the highest confidence that we include patients with true pleural sepsis. However, this investigational design, which is common in studies like ours, may have slightly affected the accuracy of the findings on the responsible pathogens.

To conclude, our study demonstrated for the first time a differential microbiological profile between the HCA and the HA patients in Greece, that could imply different needs in their treatment. This is in agreement with observations made in health-care-associated pneumonia (HCAP) and recent guidelines have suggested elimination of the term HCAP [9]. We believe the findings presented here will augment more prudent precise empirical antibiotic use among patients with HA- and HCA-pleural infection in Greece.

Ethical approval

The study was approved by the Ethics Committees of the hospitals and patients in the prospective arm signed an informed consent form.

Declarations of interest

none.

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