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Research Article

Antibiotic resistance of infectious agents associated with prior hospitalization

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Abstract

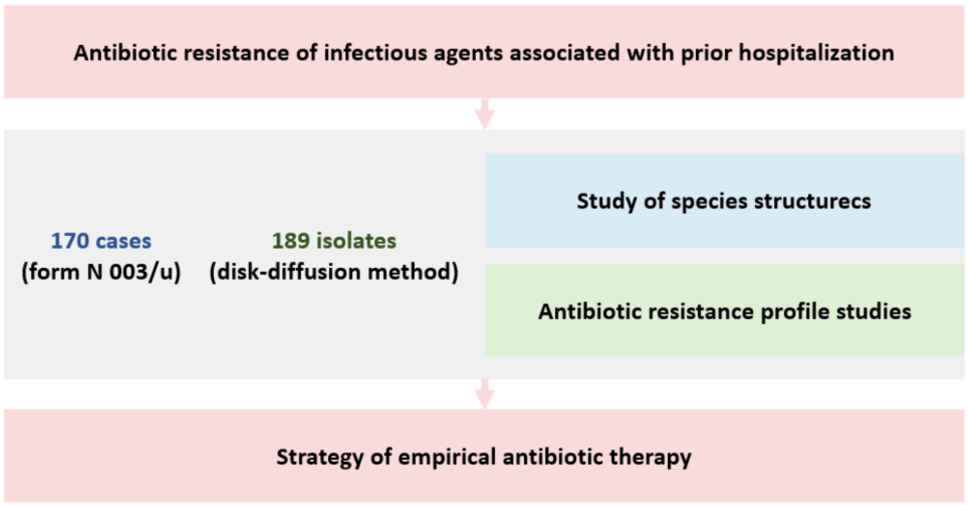
Introduction: One of the frequent causes of re-hospitalization is infectious complications due to previous colonization of patient loci by microorganisms circulating in the hospital environment. In the conditions of real clinical practice among hospital-acquired infections (HAI), it is advisable to distinguish a special group of diseases – infections associated with previous hospitalization (IPAH). Of particular scientific interest is the study of the antibiotic resistance profile of IPAH pathogens in order to determine the further strategy of empirical antibiotic therapy.

Materials and methods: A two-center descriptive study was conducted in Tomsk region. We analyzed 170 cases of IPAH according to the medical records of patients receiving medical care in inpatient settings (form N 003/u) in the period from 2019 to 2023. Identification of microorganisms was carried out by classical bacteriological method.

Results and discussion: Gram-negative bacteria (95.3%) predominated in the etiology of pneumonia associated with prior hospitalization. Among Gram-negative microorganisms, the most frequent were *K. pneumoniae, P. aeroginosa* and *K. oxytoca*. Representatives of the families *Enterobacteriaceae* (48.2%), *Staphylococcaceae* (28.9%) and *Enterococcaceae* (10.8%) predominated in the etiology of surgical infection associated with previous hospitalization. In the species structure, the key pathogens were *K. pneumoniae, S. aureus* and *E. coli.* IPAH pathogens were characterized by an unfavorable resistance profile.

Conclusion: Despite the fact that the etiological structure and antibiotic resistance profile of IPAH are similar to those of classical nosocomial infections, IPAH has important features that should certainly be taken into account when organizing medical care for this cohort of patients.

Graphical Abstract



Keywords

antibiotic resistance, antibiotic therapy, nosocomial infections, previous hospitalization

Introduction

Repeat hospitalization is considered an important indicator of the quality of health care delivery (Huepenbecker and Meyer 2022). One of the frequent causes of re-hospitalization is infectious complications due to previous colonization of patient loci by microorganisms circulating in the hospital environment (Zakaria et al. 2020; Balane et al. 2023). It is reported that in the overall structure of the causes of re-hospitalizations, infectious complications presumably related to a previous stay in a medical organization (MO) account for 42.9% (Balane et al. 2023). Hospital-acquired infections (HAI) are a common public health problem with significant biological and financial implications for both patients and MO.

The most common forms of HAI are respiratory tract infection, surgical site infection (SSI) and urinary tract infection (Lemiech-Mirowska et al. 2021). SSI were more frequently reported in patients after abdominal surgery (54.0%), orthopedic surgery (23.5%), and operative gynecology (13.2%). It has been reported that the etiologic pattern of SSI varies considerably depending on the class of surgical wound, the setting and profile of the MO, and the technique of surgical wound closure (Weiner-Lastinger et al. 2020). *S. aureus* and *E. coli* are the most frequent pathogens of SSI, with resistance levels varying significantly across regions and states.

Healthcare-associated pneumonia was first described in 2005 in the American Thoracic Society guidelines as a distinct form of nosocomial pneumonia. This concept was based on the assumption that patients who frequently seek medical care are at higher risk of contracting multidrug-resistant (MDR) pathogens and therefore need approaches to antibiotic therapy (ABT) that approximate the treatment of classic nosocomial pneumonia (NP) (Ewig et al. 2019). In the Russian Federation, the term "healthcare-associated pneumonia" has not been introduced into clinical practice; treatment of this group of patients is carried out in accordance with clinical recommendations on NP, taking into account the risk of infection with MDR pathogens. Nevertheless, "healthcare-associated pneumonia" continues to be the subject of scientific inquiry in current clinical research on antimicrobial resistance.

In the conditions of real clinical practice among HAI, it is reasonable to distinguish a special group of diseases – infections associated with previous hospitalization (IPAH) (Perfileva et al. 2023). When a patient is admitted to a MO, IPAHs are often not recognized by specialists in terms of the nosocomial nature of the infection, which predetermines a high probability of failure of empirical ABT. Given the fact that classical HAIs are caused by microorganisms with resistance to the main groups of antibacterial drugs (ABD), it is of particular scientific interest to study the antibiotic resistance profile of infectious agents in order to determine the further strategy of empirical ABT.

Materials and methods

Study design

A two-center descriptive study was conducted on the basis of Clinics of Siberian State Medical University and City Clinical Hospital No. 3 named after B.I. Alperovich (Tomsk). We analyzed 170 cases of IPAH according to the data from the medical records of patients receiving

medical care in inpatient settings (form N 003/u) in the period from 2019 to 2023. Patients older than 18 years of age with a diagnosis of "pneumonia not associated with artificial ventilation" (n=107) and "surgical infection" (n=62), with the presence of an established previous hospitalization in the MO of the city of Tomsk within the last 90 days – lasting at least 5 days for pneumonias and previous surgical intervention within the last 90 days for surgical infection were included in the study. In all patients, prior hospitalization was the cause of infection development. The study protocol was approved at the meeting of the local ethical committee of Siberian State Medical University (Minutes № 8819 of 25.10.2021). The research conditions were consistent with the requirements of the ethical and legal standards, as well as the rights, interests, and personal dignity of the research participants.

In order to assess the structure of microorganisms – etiologic agents of IPAH and the level of their antibiotic resistance, a unified registry of microorganisms was created on the online platform AMRcloud. Collection of material for bacteriologic examination was performed on the day of a patient admission prior to ABT. In case of pneumonia, the material for examination was sputum or bronchoalveolar lavage. In case of surgical infection, wound secretions, abscess secretions, abdominal fluid were taken for examination, depending on the form of infection. Identification of microorganisms was carried out by classical bacteriological method taking into account morphological, culture and biochemical properties. The studies were performed by sowing on dense nutrient media 5% blood and yolk-salt agar, Olkenitsky's and Simmons' media (Russia). The sensitivity of microbial pathogens was determined by disk-diffusion method on Mueller Hinton Agar (Russia) using Bio-Rad disks. The results were interpreted according to the EUCAST breakpoints evaluation criteria. A total of 189 isolates were analyzed in this study. The following terminology was used to describe the results of microbial sensitivity to ABP:

- «sensitive» – the activity level of the antibiotic indicates a high probability of therapeutic efficacy with a standard dosing regimen or the activity level of the drug indicates a high probability of therapeutic efficacy with increased exposure to the drug by adjusting the dosing regimen or due to its concentration in the focus of infection;
- «resistant» or «unsusceptible» – the drug activity level indicates a high probability of therapeutic failure even with increased drug exposure.

Group description

The cases were selected for the study based on the inclusion and exclusion criteria. The inclusion criteria are the following:

1. Age 18 and older.
2. Registrable IPAH forms:
   - Pneumonia not associated with invasive ventilation;
   - Surgical infection.
3. Having a documented prior hospitalization of at least days within the last 90 days for pneumonias and prior surgical intervention within the last 90 days for surgical site infections in Tomsk medical organizations.
4. Negative laboratory result for SARS-CoV-2 RNA using nucleic acid amplification techniques to rule out a new coronavirus infection.
5. No history of COVID diagnosis within the last 3 months prior to the present hospitalization.
6. Identification of the bacterial etiologic agent (positive bacteriologic culture).

The exclusion criteria are the following:

1. A patient has pneumonia associated with invasive ventilation or an infection with a localization other than those specified in the Inclusion Criteria section.
2. A patient has severe renal impairment requiring renal replacement therapy (C5 CKD).
3. A patient has severe liver dysfunction (Child-Pugh class C).
4. No HIV infection in a patient.
5. Development of superinfection in a patient during an ongoing hospitalization.
6. Cancer pathology regardless of localization.
7. Presence of concomitant disease of infectious genesis, requiring the prescription of antibiotics.
8. Referral of a patient diagnosed with IPAH to a medical organization providing medical care in outpatient conditions prior to the present hospitalization.

Statistical analysis

Case information was entered into a Microsoft Office Access database for further analysis. The data obtained in the study were evaluated from the perspective of evidence-based medicine and taking into account the requirements for statistical studies. The data were collected and stored in Microsoft Office package on the Yandex Disk cloud platform and portable media (USB flash drive). In order to assess the structure of microorganisms – etiologic agents of IPAH and the level of their antibiotic resistance, a unified registry of microorganisms was created on the online AMRcloud platform. Descriptive statistics methods were applied in the study. Qualitative features are presented in the form of absolute values (n) and fractions (%).

Results and Discussion

Gram-negative bacteria (95.3%) were predominant in the etiology of pneumonia associated with prior hospitalization (PAPH). Among Gram-negative microorganisms, the most frequent were *K. pneumoniae, P. aeroginosa* and *K. oxytoca* (Table 1).

Table 1. Etiological structure of pneumonia pathogens associated with prior hospitalization

Type of microorganism	N	%
Klebsiella pneumoniae	55	51.9
Pseudomonas aeroginosa	21	19.8
Klebsiella oxytoca	17	16.0
Staphylococcus aureus	4	3.8
Acinetobacter sp	3	2.8
Escherichia coli	2	1.9
Acinetobacter baumannii	1	0.9
Enterobacter aerogenes	1	0.9
Klebsiella ozaenae	1	0.9
Staphylococcus haemolyticus	1	0.9
Total	106	100

K. pneumoniae isolates showed high levels of resistance to cefotaxime (90.5%), ceftriaxone (86.7%), ceftazidime (85.1%), and cefepime (66.7%). Resistance to amoxicillin+clavulanic acid was 81.0%. Resistance to fluoroquinolones, ciprofloxacin and levofloxacin, was exhibited by 58.3% and 27.8% of isolates, respectively. There were isolated pathogens unsusceptible to aminoglycosides, gentamicin and amikacin, at 35.5% and 29.0%, respetively. Resistance to carbapenems (imipenem, meropenem and ertapenem) was exhibited by 9.8%, 4.4% and 41.7% of all isolates, respectively (Table 2).

Table 2. Sensitivity of *K. pneumoniae* to antibacterial drugs in patients with pneumonia

International nonproprietary name	Anatomo-therapeutic-chemical classification	S, %	I, %	R, %
Amikacin	Aminoglycosides	71.00	0.0	29.0
Amoxicillin + clavulanic acid	Penicillins	19.0	0.0	81.0
Cefepime	IV generation cephalosporins	33.3	0.0	66.7
Cefotaxime	III generation cephalosporins	9.5	0.0	90.5
Ceftazidime	III generation cephalosporins	14.9	0.0	85.1
Ceftriaxone	III generation cephalosporins	13.3	0.0	86.7
Ciprofloxacin	Fluoroquinolones	41.7	0.0	58.3
Ertapenem	Carbapenems	50.0	8.3	41.7
Gentamicin	Aminoglycosides	64.5	0.0	35.5
Imipenem	Carbapenems	90.2	0.0	9.8
Levofloxacin	Fluoroquinolones	72.2	0.0	27.8
Meropenem	Carbapenems	88.9	6.7	4.4

Among the identified pathogens of *P. aeroginosa*, resistance to the antimicrobials with activity against *P. aeruginosa*, cephalosporins, ceftazidime and cefepime, was observed at 88.9% and 81.3%, respectively; 64.7% of isolates were insensitive to ciprofloxacin. *P. aeroginosa* resistance to amikacin was detected in 18.2% of cases. Of note, carbapenem resistance was at 33.3% to meropenem and 37.5% to imipenem (Table 3).

Table 3. Sensitivity of *P. aeroginosa* to antibacterial drugs in patients with pneumonia

International nonproprietary name	Anatomo-therapeutic-chemical classification	S, %	I, %	R, %
Cefepime	IV generation cephalosporins	12.5	6.2	81.3
Ceftazidime	III generation cephalosporins	11.1	0.0	88.9
Ciprofloxacin	Fluoroquinolones	35.3	0.0	64.7
Imipenem	Carbapenems	56.3	6.2	37.5
Meropenem	Carbapenems	55.6	11.1	33.3

K. oxytoca was characterized by a high level of resistance to cephalosporins. Thus resistance to ceftazidime, cefotaxime and cefepime was 68.8%, 56.3% and 11.1%, respectively. There was resistance to ciprofloxacin at 16.7%. Carbapenems resistance ranged from 20.0% (ertapenem) to 50.0% (meropenem). Aminoglycosides were the most active against *K. oxytoca*, and all isolates were sensitive to both gentamicin and amikacin (Table 4).

Table 4. Sensitivity of *K. oxytoca* to antibacterial drugs in patients with pneumonia

International nonproprietary name	Anatomo-therapeutic-chemical classification	S, %	I, %	R, %
Amikacin	Aminoglycosides	100.0	0.0	0.0
Cefepime	IV generation cephalosporins	88.9	0.0	11.1
Cefotaxime	III generation cephalosporins	43.7	0.0	56.3
Ceftazidime	III generation cephalosporins	31.2	0.0	68.8
Ciprofloxacin	Fluoroquinolones	83.3	0.0	16.7
Ertapenem	Carbapenems	80.0	0.0	20.0
Gentamicin	Aminoglycosides	100.0	0.0	0.0
Imipenem	Carbapenems	66.6	0.0	33.3
Meropenem	Carbapenems	50.0	0.0	50.0

Representatives of the families Enterobacteriaceae (48.2%), Staphylococcaceae (28.9%) and Enterococcaceae (10.8%) predominated in the etiology of surgical infection associated with prior hospitalization (SIAPH). In the species structure, the key pathogens were *K. pneumoniae, S. aureus* and *E. coli* (Table 5).

Table 5. Etiologic structure of surgical infectious agents associated with prior hospitalization

Type of microorganism	N	%
Klebsiella pneumoniae	19	22.9
Staphylococcus aureus	19	22.9
Escherichia coli	14	16.9
Enterococcus faecalis	7	8.4
Klebsiella oxytoca	6	7.2
Pseudomonas aeroginosa	6	7.2
Staphylococcus epidermidis	3	3.6
Enterococcus faecium	2	2.4
Staphylococcus haemolyticus	2	2.4
Streptococcus sp	2	2.4
Acinetobacter baumannii	1	1.2
Acinetobacter sp	1	1.2
Proteus mirabilis	1	1.2
Total	83	100

K. pneumoniae was characterized by a high level of resistance to amoxicillin+clavulanic acid (90.0%). A high incidence of strain resistance was found for cefotaxime, ceftazidime and cefepime, 76.5%, 70.6% and 70.6%, respectively. The low sensitivity of isolates to fluoroquinolones is worth mentioning separately. Resistance to ciprofloxacin was 70.6%, while resistance to levofloxacin was 62.5%. Among carbapenems, meropenem was found to have the highest sensitivity (58.8%). The sensitivity of *K. pneumoniae* to aminoglycosides was 60.0% for amikacin and 66.7% for gentamicin (Table 6).

Table 6. Sensitivity of *K. pneumoniae* to antibacterial agents in patients with surgical infection

International nonproprietary name	Anatomo-therapeutic-chemical classification	S, %	I, %	R, %
Amikacin	Aminoglycosides	60.0	0.0	40.0
Amoxicillin + clavulanic acid	Penicillins	10.0	0.0	90.0
Cefepime	IV generation cephalosporins	29.4	0.0	70.6
Cefotaxime	III generation cephalosporins	23.5	0.0	76.5
Ceftazidime	III generation cephalosporins	29.4	0.0	70.6
Ciprofloxacin	Fluoroquinolones	29.4	0.0	70.6
Ertapenem	Carbapenems	30.8	0.0	69.2
Gentamicin	Aminoglycosides	66.7	0.0	40.0
Imipenem	Carbapenems	50.0	33.3	16.7
Levofloxacin	Fluoroquinolones	37.5	0.0	62.5
Meropenem	Carbapenems	58.8	17.7	23.5

S. aureus isolates showed resistance to erythromycin (13.3%), gentamicin (18.2%), clindamycin (22.2%), and ciprofloxacin (36.4%). All pathogens were sensitive to vancomycin and linezolid. Methicillin-resistant *S. aureus* (MRSA) accounted for 25.0% of the isolates (Table 7).

Table 7. Sensitivity of *S. aureus* to antibacterial agents in patients with surgical infection

International nonproprietary name	Anatomo-therapeutic-chemical classification	S, %	I, %	R, %
Cefoxitin	Cephalosporins of II generation	75.0	0.0	25.0
Ciprofloxacin	Fluoroquinolones	54.5	9.1	36.4
Clindamycin	Lincosamides	77.8	0.0	22.2
Gentamicin	Aminoglycosides	81.8	0.0	18.2
Linezolid	Oxazolidinone	100.0	0.0	0.0
Vancomycin	Glycopeptides	100.0	0.0	0.0

E. coli showed resistance to cephalosporins (72.7% – to cefepime, 83.3% – to cefotaxime, 66.7% – to ceftazidime). Among fluoroquinolones, ciprofloxacin (66.7%) showed a higher level of resistance compared to levofloxacin (40.0%). Of note, all isolates were insensitive to amoxicillin+clavulanic acid. Ertapenem resistance was 12.5%, with all pathogens being sensitive to imipenem and meropenem. Sensitivity to amikacin and gentamicin was 100.0% and 85.7%, respectively (Table 8).

Table 8. Sensitivity of *E. coli* to antibacterial agents in patients with surgical infection

International nonproprietary name	Anatomo-therapeutic-chemical classification	S, %	I, %	R, %
Amikacin	Aminoglycosides	100.	0.0	0.0
Amoxicillin + clavulanic acid	Penicillins	0.0	0.0	100.0
Cefepime	IV generation cephalosporins	27.3	0.0	72.7
Cefotaxime	III generation cephalosporins	16.7	0.0	83.3
Ceftazidime	III generation cephalosporins	33.3	0.0	66.7
Ciprofloxacin	Fluoroquinolones	33.3	0.0	66.7
Ertapenem	Carbapenems	75.0	12.5	12.5
Gentamicin	Aminoglycosides	85.7	0.0	14.3
Imipenem	Carbapenems	100.	0.0	0.0
Levofloxacin	Fluoroquinolones	60.0	0.0	40.0
Meropenem	Carbapenems	91.7	8.3	0.0

Pneumonia remains the most frequent form of HAI. It is worth mentioning that in clinical practice 65% of pneumonia cases are not associated with artificial lung ventilation (Mitchell et al. 2019). Pneumonia can be caused by different pathogens, which is determined by a large number of factors – the patient's length of stay in the MO, the type of MO, the stay in the anesthesiology and intensive care unit, and the strategy of ABD use in the MO (Rachina et al. 2023). The etiologic structure of the IPAH established by our study generally corresponds to the classical nosocomial pathogens of pneumonias. Thus, the most frequent NP pathogens in the Russian Federation are *K. pneumoniae* (25.7%), *P. aeruginosa* (23.4%) and *A. baumannii* (19.1%) (Kuzmenkov et al. 2021). In our study, *A. baumannii* did not play a key role in the etiology of PAPH, which is probably due to the fact that *A. baumannii* is one of the leading causative agents of ventilator-associated pneumonias, which were not investigated in this study. It is interesting to note that in our study *K. oxytoca* occupied the third position in the etiology of PAPH, being quite a frequent infectious agent in patients. At the same time, in the general structure of NP etiologic agents in the Russian Federation, this pathogen is not marked as a key one, which, apparently, is associated with local microbiological features. However, a number of studies also demonstrate the important role of this pathogen in the current etiology of HAI (Neog et al. 2021; Yang et al. 2022). Considering the etiologic

structure of NP pathogens in the Siberian Federal District, *K. oxytoca* occupies the 11th position.

Assessing the antibiotic resistance profile of PAPH agents, it should be noted that *K. pneumoniae* was characterized by a higher level of resistance to cefolosporins compared to *K. oxytoca*. Thus, the resistance of *K. pneumoniae* isolates to this group of ABP reached 90.5%, which is consistent with the all-Russian data (90.6%). At the same time in Tomsk region, *K. pneumoniae* in the group of PAPH is more sensitive to fluoroquinolones, in particular to ciprofloxacin – 58.3% against the all-Russian figure of 82.2%. A similar trend is observed in the group of aminoglycosides – according to the study, *K. pneumoniae* resistance reached 35.5%, while in the Russian Federation among nosocomial strains of *K. pneumoniae* unsusceptible to aminoglycosides reaches 62.3%. In general, amikacin compared to gentamicin demonstrated greater activity against *K. pneumoniae*, both according to our study and according to the data of microbiological monitoring in the Russian Federation. In our study, resistance of *K. pneumoniae* to carbapenems was significantly lower than on the all-Russian level. *K. oxytoca*, according to the results of this study, showed higher levels of resistance to the main groups of ABD compared to the data for the Russian Federation. This pathogen showed absolute sensitivity only to aminoglycosides. *P. aeroginosa* had a high incidence of resistance to cephalosporins, so in our study, unsusceptible of isolates reached 88.9%, while in the Russian Federation this percentage was 53.1%. At the same time, the level of resistance to ciprofloxacin was generally in line with the all-Russian rate of 64.7% vs. 63.4%. It should be noted that in our study *P. aeroginosa* showed resistance to amikacin in 18.2% of cases, while in the Russian Federation this pathogen was unsusceptible to amikacin in 44.1% of cases (Kuzmenkov et al. 2021). A similar pattern was observed in the carbapenems group – resistance of isolates did not exceed 37.5%.

In the etiologic structure of SIAPH, *K. pneumoniae* and *S. aureus* were the leading pathogens. In the structure of SIAPH in the Russian Federation, *P. aeruginosa* occupies the first position, while *K. pneumoniae* is in third place (Kuzmenkov et al. 2021). In our study, *K. pneumoniae* showed a lower incidence of resistance to cephalosporins (76.5%) compared to the nationwide trend of SSI (86.5%). The same pattern was observed for fluoroquinolones. The isolates were characterized by a higher level of resistance to carbapenems and aminoglycosides compared to nosocomial isolates of *K. pneumoniae* SSI. *S. aureus* has a more favorable sensitivity profile to the main groups of ABD compared to classical nosocomial isolates. Certainly, the absolute sensitivity of pathogens to vancomycin and linezolid and not high frequency of MRSA identification are positive aspects of the study. *E. coli* in the etiology of SIAPH has been a problematic pathogen. The level of its resistance to cephalosporins reached 83.3%, in particular to cefotaxime, which is higher than in the Russian Federation (68.3%). Absolute resistance of the pathogen to amoxicillin+clavulanic acid was observed, while in the Russian Federation 40.1% of *E. coli* isolates causing SIAPH are sensitive to this ABP (Kuzmenkov et al. 2021). It should be noted that the pathogen showed absolute sensitivity to imipenem and ertapenem, as well as to amikacin.

Conclusion

K. pneumoniae, P. aeruginosa and *K. oxytoca* predominated in the species structure of PAPH. *K. pneumoniae, S. aureus* and *E. coli* became the predominant pathogens in the etiologic structure of SIAPH. *K. pneumoniae* showed a high level of resistance to penicillins and cephalosporins. *P. aeroginosa* and *K. oxytoca* were characterized by high resistance to cephalosporins and fluoroquinolones. *S. aureus* had a favorable sensitivity profile to the main groups of antibiotics. Despite the fact that the etiological structure of the IPAH and antibiotic resistance profile are similar to classical nosocomial infections, the IPAH have important features, which, of course, should be taken into account when organizing medical care for this cohort of patients.

Conflict of interest

The authors have declared that no competing interests exist.

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Data availability

All of the data that support the findings of this study are available in the main text.

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