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Coronavirus Pademic

Profile of co-occurring or secondary infections among COVID-19 patients with HBOT: a single-center retrospective study

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Abstract

Introduction: This study was designed to describe the profile of co-occurring or secondary infections in hospitalized coronavirus disease 2019 (COVID-19) patients undergoing hyperbaric oxygen therapy (HBOT) and those without.

Methodology: Out of 716 COVID-19 patients, 79 cases of co-occurring or secondary infections were included. These patients were categorized into two groups based on their usage of HBOT. The basic information and laboratory examinations, especially pathogen-related results were collected from the medical records. The rate of co-occurring or secondary infections, distribution of pathogens, infection sites, and results of antimicrobial susceptibility testing were analyzed.

Results: Among the 79 COVID-19 patients examined, there were 73 cases of infections, including 58 co-occurring infections, 14 secondary infections, and 1 mixed infection in the non-HBOT group. There were 6 cases with co-occurring or secondary infections in the HBOT group. Influenza virus was predominant in the co-occurring or secondary infections of COVID-19 patients, but it was not detected in patients undergoing HBOT. *Klebsiella pneumoniae*, *Corynebacterium striatum*, and *Acinetobacter baumannii* were the main strains isolated among patients with HBOT. The multidrug-resistant organisms (MDROs) strains of *Escherichia coli*, *Klebsiella aerogenes*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Enterococcus faecium* were detected from COVID-19 patients treated with HBOT.

Conclusions: This study described the profile of in-hospital co-occurring or secondary infections in COVID-19 patients from North China. Management of the co-occurring or secondary infections, especially MDROs infections treated with HBOT, including but not limited to COVID-19, should be strengthened.

Key words: coronavirus disease-19 (COVID-19); hyperbaric oxygen therapy (HBOT); co-occurring infections; secondary infections; multidrug-resistant organisms (MDROs).

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has posed various clinical challenges of severe or fatal complications in the last three years [1]. Oxygen therapy has remained an important method for treating respiratory insufficiency in COVID-19 patients [2]. Hyperbaric oxygen therapy (HBOT), using pure oxygen under increased pressure to augment oxygen levels in the blood and tissue, has been proposed as an effective oxygenation treatment for patients with COVID-19 [3]. It is also reported that HBOT can improve the quality of life, quality of sleep, psychiatric, and pain symptoms of patients suffering from long COVID. [4] Meanwhile, HBOT has been used, either alone or as an adjunct treatment, in the clinical management of inflammatory conditions by

reoxygenation and enhancing the bactericidal activity of antibiotics [5]. According to a review, HBOT may also improve antibiotic treatment of bacterial biofilms by reviving the dormant bacteria, thus making them susceptible to antibiotics by means of reoxygenation [6]. Patients hospitalized with COVID-19 were reported to have a high incidence of co-occurring or secondary infections [7]. However, HBOT has not been scientifically and sufficiently evaluated for co-occurring or secondary infections in the COVID-19 population. To the best of our knowledge, the prevalence, incidence, and characteristics of co-occurring or secondary infections in COVID-19 patients treated with HBOT have not been reported. Therefore, a retrospective single-center study was performed to explore the profile of the co-occurring or secondary infections in COVID-19 patients treated with or without HBOT to provide the necessary evidence for clinicians in the management of infections among COVID-19 patients, and further viral respiratory infections with HBOT.

Methodology

Participants and design

The medical records of 716 consecutive COVID-19 patients admitted to Shanxi Bethune Hospital from December 8, 2022, to January 31, 2023, were thoroughly examined. All patients fulfilled the COVID-19 diagnostic criteria [8]. Patients with malignancies, blood transfusion administration within the last six months, delivery during hospitalization, and incomplete medical records were excluded. The HBOT procedure was 100% O_2 at 2.8 bar in a closed hyperbaric chamber. All subjects were divided into two groups based on the use of HBOT, which was determined according to the assessment of patients' conditions. A total of 79 eligible patients with co-occurring or secondary infections; 6 out of 23 from the HBOT group, and 73 out of 693 from the non-HBOT group were included in the study. The definitions of co-occurring and secondary infection were referred to in a previously published review and have been used in numerous clinical studies [9]. Co-occurring infections were diagnosed within two days after admission, and secondary infections occurred more than two days after admission. The study was conducted in accordance with the Declaration of Helsinki and received approval from the Hospital Clinical Research Ethics Committee of Shanxi Bethune Hospital, with the requirement for consent waived for all participants (YXLL-2023-254).

Data extraction and description of pathogens and bacterial-related profile

The demographic data and clinical information, especially pathogen-related results of 79 COVID-19 patients, were extracted from the medical records. All pathogens from patients were identified by using standard techniques in VITEK2 compact system (BioMerieux, Inc., Lyon, France), mass spectrometry (Bruker, Saarbrücken, Germany), and multiplex respiratory pathogen detection (IgM; Indirect immunofluorescence assaym IFA; Euroimmun, Lübeck, Germany) from the samples of serum, sputa, endobronchial secretions or midstream urine. The antimicrobial susceptibility testing was performed in the VITEK2 compact system with broth dilution method and reported as minimum inhibitory concentration (MIC). The antibiotics were classified into related categories according to the guiding principles of antimicrobial stewardship [10].

Statistical analysis

Continuous variables with normal distribution were presented as the mean, followed by standard deviation. The abnormal distribution of continuous variables was presented as the median and the interquartile range from the first to the third quartile (Q1–Q3). The Shapiro-Wilk test was used to test the normality of continuous variables. Students' t-tests and Wilcoxon rank-sum tests were used for normal and non-normal distributed quantitative data. Chi-square or Fisher's exact test analyzed categorical variables. p values below 0.05 were deemed statistically significant. Given the observational nature of the study, coupled with the small sample size and low incidence of co-/secondary infections, conducting a multivariate analysis was not feasible. Consequently, the p values reported in this study are nominal and should not be interpreted as definitive for statistical inference. Stata SE 13 (StataCorp, College Station, TX, USA; LPSerial number 401306302851), R software version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria), and easy-R (www.empowerstats.com) were used for statistical analysis. GraphPad was used to generate figures.

Results

Basic characteristics of the subjects

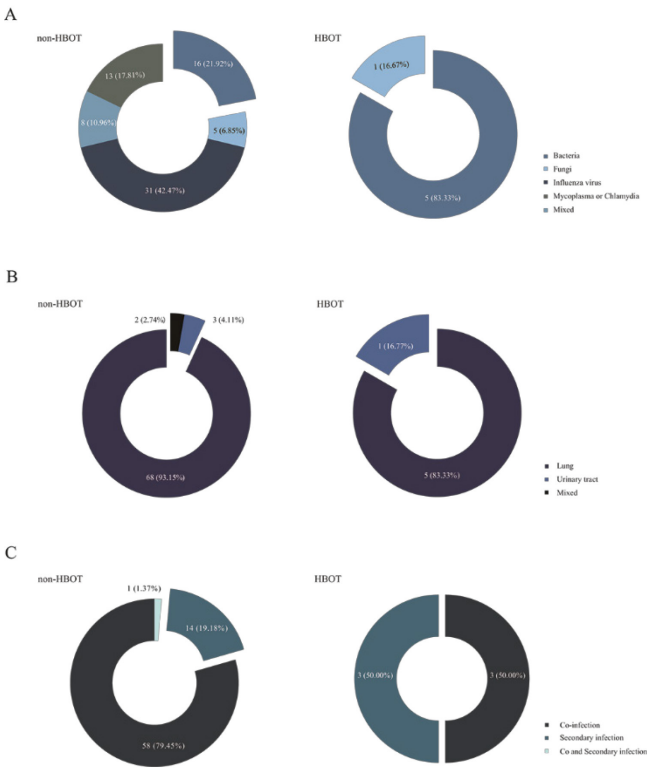
The data of 79 COVID-19 patients with co-occurring or secondary infections under HBOT or not were retrospectively analyzed. The basic demographic and clinical characteristics of the subjects are

summarized in Table 1. The gender composition was comparable between the non-HBOT and HBOT groups, while the age was significantly different between the two groups ($p = 0.002$) with average age of 72.30 years and 58.00 years in non-HBOT and HBOT groups, respectively. There were no notable differences in smoking, hypertension, coronary heart disease, stroke, diabetes, renal dysfunction, and liver dysfunction between the two groups. Neither oxygen saturation nor disease severity showed significant differences. The treatment protocol of oxygen therapy differed between the two groups ($p = 0.013$).

Distribution of pathogens in the COVID-19 subjects with co-occurring or secondary infections

Distribution of pathogens in the COVID-19 subjects with co-occurring or secondary infections is summarized in Table 2 and Figure 1. 73 cases of infections, including multidrug-resistant organisms (MDROs), 58 co-occurring infections, 14 secondary infections, and 1 mixed infection occurred in the non-HBOT group, which were caused by bacteria, fungi, influenza virus, mycoplasma or chlamydia, and mixed pathogens. Among the non-HBOT group, influenza virus infections accounted for most infected cases, followed by bacterial infections, and mixed infections. In the HBOT group, there were three cases of co-occurring infections and an additional three cases of secondary infections, involving a total of five bacterial infections and one fungal infection. The infections primarily attacked the lungs, with a few cases of urinary tract or mixed infections. The bacterial infection proportion in patients of the HBOT group surpassed that of the non-HBOT group ($p = 0.012$). Detailed information is provided in Figure 2.

Figure 1. Overview of co-occurring or secondary infections among hospitalized COVID-19 patients. A, distribution of pathogenic microorganisms; B, localizations of infections; C, breakdown of co-occurring or secondary infections.



COVID-19, coronavirus disease 2019; HBOT, hyperbaric oxygen therapy.

Table 1. General characteristics and clinical treatment of COVID-19 subjects with co-occurring or secondary infections.

Characteristics		All (n = 79)	non-HBOT (n = 73)	HBOT (n = 6)	Statistics	*p* value
Gender	Male	43 (54.43)	40 (54.79)	3 (50.00)	$\chi^2 = 0.05$	0.821
Age	Mean ± sd	71.22±16.09	72.30 ± 15.99	58.00 ± 11.35	t = 2.14	0.035
	Min–max	30–91	30–91	48–73		
Smoking n (%)	No	59 (74.68)	54 (73.97)	5 (83.33)	$\chi^2 = 0.29$	0.863
	Yes	19 (24.05)	18 (24.66)	1 (16.67)		
	Unreported	1 (1.27)	1 (1.37)	0 (0.00)		
Oxygen saturation (%)	Mean ± sd	93.08 ± 4.15	93.16 ± 4.08	92.15 ± 5.27	t = 0.570	0.571
Diseases severity	Moderate	23 (29.11)	19 (26.03)	4 (66.67)	$\chi^2 = 4.58$	0.101
	Sever	49 (62.03)	47 (64.38)	2 (33.33)		
	Critical	7 (8.86)	7 (9.59)	0 (0.00)		
Hypertension	n (%)	36 (45.57)	35 (47.95)	1 (16.67)	$\chi^2 = 2.19$	0.139
Coronary heart disease	n (%)	7 (8.86)	7 (9.59)	0 (0.00)	$\chi^2 = 0.63$	0.427
Stroke	n (%)	18 (22.78)	16 (21.92)	2 (33.33)	$\chi^2 = 0.411$	0.522
Diabetics	n (%)	20 (25.32)	19 (26.03)	1 (16.67)	$\chi^2 = 0.257$	0.612
Renal dysfunction	n (%)	8 (10.13)	8 (10.96)	0 (0.00)	$\chi^2 = 0.73$	0.392
Liver dysfunction	n (%)	12 (15.19)	12 (16.44)	0 (0.00)	$\chi^2 = 1.16$	0.281
Usage of oxygen therapy	n (%)	73 (92.41)	69 (94.52)	4 (66.67)	$\chi^2 = 6.13$	0.013

COVID-19, coronavirus disease 2019; HBOT, hyperbaric oxygen therapy; NLR, neutrophil to lymphocyte ratio; q1, 1st quartile; q3, 3rd quartile; sd, standard deviation.

Table 2. Distribution of pathogens detected from COVID-19 subjects.

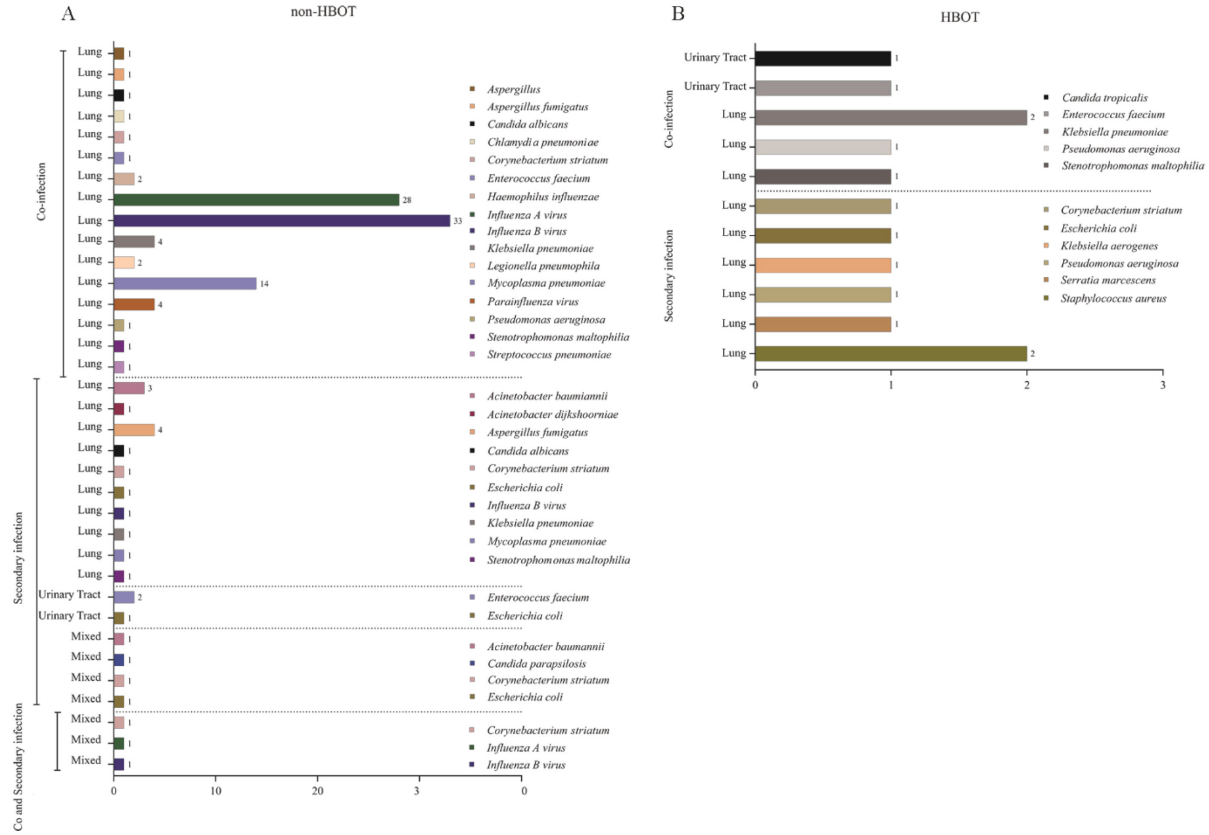
		All (n = 79)	non-HBOT (n = 73)	HBOT (n = 6)	χ^2	*p* value
Pathogen composition ratio n (%)	Bacteria	21 (26.58)	16 (21.92)	5 (83.33)	12.84	0.012
	Fungi	6 (7.59)	5 (6.85)	1 (16.67)		
	Influenza virus	31 (39.24)	31 (42.47)	0 (0.00)		
	M/C	8 (10.13)	8 (10.96)	0 (0.00)		
	Mixed	13 (16.46)	13 (17.81)	0 (0.00)		
Site of infections n (%)	Lung	73 (92.41)	68 (93.15)	5 (83.33)	1.95	0.377
	Urinary tract	4 (5.06)	3 (4.11)	1 (16.67)		
	Mixed	2 (2.53)	2 (2.74)	0 (0.00)		

COVID-19, coronavirus disease 2019; HBOT, hyperbaric oxygen therapy; M/C, *Mycoplasma* or *Chlamydia*

Distribution of bacterial strains and detection of MDROs in COVID-19 subjects

Distribution of the14 bacteria strains isolated from 21 COVID-19 subjects (16 from non-HBOT and 5 from HBOT) and their Gram staining results is presented in Table 3. Among the 14 bacteria strains, *Klebsiella pneumoniae* (*K. pneumoniae*) was the primary strain followed by *Corynebacterium striatum* (*C. striatum*), *Acinetobacter baumannii* (*A. baumannii*), *Escherichia coli* (*E. coli*), *Enterococcus faecium* (*E. faecium*), *Pseudomonas aeruginosa* (*P. aeruginosa*), and *Stenotrophomonas maltophilia* (*S. maltophilia*). These were the top seven strains isolated; *C. striatum* and *E. faecium* were Gram-positive and the other five strains were Gram-negative. Furthermore, the results of antimicrobial susceptibility testing and detection of MDROs are summarized in Table 4. Many bacterial strains exhibited extensive resistance to penicillins, cephalosporins, β-lactamides/β-lactamase inhibitors, carbapenems, aminoglycosides, quinolones, furans, etc. Five MDRO strains of *E. coli*, *Klebsiella aerogenes* (*K. aerogenes*), *Staphylococcus aureus* (*S. aureus*), *P. aeruginosa*, and *Enterococcus faecium* (*E. faecium*) were detected in the group of HBOT. The strains of *E. coli*, *Streptococcus pneumoniae* (*S. pneumoniae*), and *A. baumannii* were identified as MDROs from the non-HBOT group.

Figure 2. Pathogenic microorganism of co-occurring or secondary infections among hospitalized COVID-19 patient.



COVID-19, coronavirus disease 2019; HBOT, hyperbaric oxygen therapy.

Table 3. Distribution of isolated bacterial strains from COVID-19 subjects with bacterial infections.

Ranking	Bacterial strains	G-/G+	Isolates (%) (n = 42)
1	*Klebsiella pneumoniae* (*K. pneumoniae*)	G-	7 (16.66)
2	*Corynebacterium striatum* (*C. striatum*)	G+	6 (14.28)
3	*Acinetobacter baumannii* (*A. baumannii*)	G-	5 (11.90)
4	*Escherichia coli* (*E. coli*)	G-	4 (9.52)
5	*Enterococcus faecium* (*E. faecium*)	G+	4 (9.52)
6	*Pseudomonas aeruginosa* (*P. aeruginosa*)	G-	3 (7.14)
7	*Stenotrophomonas maltophilia* (*S. maltophilia*)	G-	3 (7.14)
8	*Staphylococcus aureus* (*S. aureus*)	G+	2 (4.76)
9	*Legionella pneumophila* (*L. pneumophila*)	G-	2 (4.76)
10	*Haemophilus influenzae* (*H. influenzae*)	G-	2 (4.76)
11	*Klebsiella aerogenes* (*K. aerogenes*)	G-	1 (2.38)
12	*Serratia marcescens* (*S. marcescens*)	G-	1 (2.38)
13	*Acinetobacter dijkshoorniae*	G-	1 (2.38)
14	*Streptococcus pneumoniae* (*S. pneumoniae*)	G+	1 (2.38)

COVID-19, coronavirus disease 2019; G+, Gram-positive; G-, Gram-negative.

Table 4. Results of antimicrobial susceptibility test and detection of MDROs.

Group	Bacterial strains	Resistant antimicrobials and corresponding categories
HBOT	*Escherichia coli* (*E. coli*)	1. Penicillins: ampicillin 2. Quinolones: ciprofloxacin, levofloxacin 3. Sulfonamides: compound sulfamethoxazole
	Klebsiella aerogenes (*K. aerogenes*)	1.Penicillins: ampicillin 2. Cephalosporins: ceftriaxone, cefepime, cefazolin 3. Cephamycins: cefoxitin 4. β-Lactamides/β-Lactamase inhibitors: amoxicillin/corylic acid 5. Monobactams: aztreonam 6. Furans: nitrofurantoin
	Staphylococcus aureus (*S. aureus*)	1. Cephalosporins: cefazolin 2. Cephamycins: cefoxitin 3. β-lactamides/β-lactamase inhibitors: amoxicillin/corylic acid 4. Furans: nitrofurantoin
	Pseudomonas aeruginosa (*P. aeruginosa*)	1. Cephalosporins: cefazolin, ceftazidime, cefepime 2. β-lactamides/β-lactamase inhibitors; piperacillin/tazobactam 3. Carbapenems: imipenem, meropenem 4. Monobactams: aztreonam 5. Aminoglycosides: tobramycin 6. Quinolones: ciprofloxacin
	Enterococcus faecium (*E. faecium*)	1. Penicillins: penicillin, ampicillin 2. Aminoglycosides: gentamicin, streptomycin 3. Quinolones: ciprofloxacin, levofloxacin 4. Macrocyclic lactones: erythromycin 5. Furans: nitrofurantoin
NON-HBOT	*Escherichia coli* (*E. coli*)	1. Penicillins: ampicillin 2. Cephalosporins: cefazolin, ceftriaxone, cefepime 3. Monobactams: aztreonam 4. Quinolones: ciprofloxacin, levofloxacin 5. Sulfonamides: compound sulfamethoxazole
	Escherichia coli (*E. coli*)	1. Penicillins: ampicillin, piperacillin 2. Cephalosporins: cefazolin 3. β-lactamides/β- lactamase inhibitors: ampicillin/sulbactam 4. Quinolones: levofloxacin 5. Sulfonamides: compound sulfamethoxazole
	Streptococcus pneumoniae (*S. pneumoniae*)	1. Penicillins: penicillin 2. β-lactamides/β-lactamase inhibitors: amoxicillin 3. Cephalosporins: cefotaxime, ceftriaxone 4. Tetracyclines: tetracycline 5. Macrocyclic lactones: erythromycin 6. Sulfonamides: compound sulfamethoxazole
	Acinetobacter baumannii (*A. baumannii*)	1. Cephalosporins: cefazolin, ceftazidime, ceftriaxone, cefepime 2. β-lactamides/β-lactamase inhibitors: ampicillin/sulbactam, piperacillin/tazobactam, cefoperazone/sulbactam 3. Carbapenems: imipenem, meropenem 4. Aminoglycosides: gentamicin, tobramycin, amikacin 5. Quinolones: ciprofloxacin

HBOT, hyperbaric oxygen therapy; MDROs, multidrug-resistant organisms

Discussion

The novel coronavirus, SARS-CoV-2, emerged in December 2019 and has since caused the COVID-19 pandemic. A high rate of co-occurring or secondary infections often occurs in patients hospitalized with COVID-19 [7]. HBOT has been proposed as an effective oxygenation treatment for patients with COVID-19 [3]. Herein, a single-center observational study displayed the entire profile of co-occurring or secondary infections in COVID-19 patients treated with HBOT for the first time. The co-occurring or secondary infections were diagnosed in 79 (11.03%) out of 716 patients, which is slightly higher than the rate in a tertiary-care hospital in Italy, where 68 patients (9.3%) developed secondary infections among 731 COVID-19 patients [7]. The co-occurring or secondary infections mostly attacked the lungs, with a few cases of urinary tract infections or a mixture of the two infections in the targeted population. No bloodstream infections were detected in our study. However, bloodstream infections were reported in 7.9% of COVID-19 patients in Italy [7]. The most common pathogen detected from COVID-19 subjects was the influenza virus. A possible cause is that the influenza virus always causes seasonal epidemics in winter, which coincided with the time span of this study [11].

The second most common infection detected from the target patients was bacterial infections, which occurred in 26.58% of the 79 COVID-19 patients with infections. The analysis of isolated bacterial strains displayed that Gram-negative pathogens *K. pneumoniae*, *A. baumannii*, *E. coli*, *P. aeruginosa*, *S. maltophilia*; and Gram-positive pathogens *C. striatum* and *E. faecium*; were the main pathogenic bacteria of the co-occurring or secondary infections among the COVID-19 patients. *K. pneumoniae* was the leading strain among all the isolated strains in COVID-19 subjects, which was consistent with the report that *K. pneumoniae* has long been one of the most common nosocomial pathogens in the world [12]. Even though *K. pneumoniae* was not identified as MDROs in our study, we should bear in mind that the species is naturally resistant to penicillins and often carries acquired resistance to multiple antimicrobials [12]. *C. striatum* was the second major pathogenic bacteria, which is empirically treated with penicillin and glycopeptides in general and there are no standard sensitivity test results for *C. striatum* so far. As an opportunistic pathogen, *C. striatum* strains were described as saprophytic microorganisms colonizing nasal mucosa and the skin of healthy individuals and non-pathogenic to humans in the past [13]. However, the in-hospital infections and nosocomial outbreaks caused by antimicrobial strains have been increasing worldwide in recent years [14]. Our observations also provided some evidence that *C. striatum* caused more infections in COVID-19 subjects.

Antimicrobial drug resistance in bacteria and fungi are some of the major threats to global health, which cause excess morbidities and mortalities. MDROs were defined as acquiring non-susceptibility to at least one agent in three or more antimicrobial categories [15]. The "ESKAPE" pathogens (*E. faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, and *Enterobacter* species) were first proposed in 2008 and remained the leading causes of MDROs infections all over the world [16]. Even though there was a subtle difference in strains of MDROs between groups of HBOT and non-HBOT, MDROs detected from COVID-19 subjects in the present study were substantially consistent with the predominant strains worldwide. The results of antimicrobial multidrug-resistant testing showed that many bacterial strains exhibited relatively extensive resistance to penicillins, cephalosporins, β-lactamides/β-lactamase inhibitors, carbapenems, aminoglycosides, quinolones and so on. The emergence of multidrug resistance is undoubtedly multifactorial. In addition to bacterial tolerance to antibiotics and host defense mechanisms, it may be particularly related to the high rate of antimicrobial agent utilization in the circumstances of COVID-19 treatment [17]. Management of infections caused by MDROs is challenging, and a multidisciplinary approach, especially optimized use of antimicrobials, is the key to achieve successful clinical outcomes [18].

HBOT is a technique in which the patient is exposed to 100% oxygen (O_2) for a determined period of time in a special chamber at higher than atmospheric pressure [5]. HBOT has been proven to offer valuable advantages, either alone or as an adjunct treatment, for patients with infectious diseases [5,19–20] A study reported that HBOT could significantly enhance the effect of tobramycin against *P. aeruginosa* aggregate isolates from cystic fibrosis patients in vitro, which was attributed to increased O_2 levels leading to increased growth and thus increased uptake of and killing by tobramycin [21]. Another study provided evidence that HBOT has significant anti- *S. aureus* effects through direct bacterial killing, antibiotic potentiation, and polymorphonuclear leukocyte enhancement [22]. A previous study concluded that HBOT exerts antimicrobial effects through three main mechanisms, including direct bactericidal effects, enhancing the immune system, and synergistic effects with certain

antimicrobial agents [5]. Meanwhile, HBOT provides significant benefits in inducing neuroplasticity and improving cognitive, psychiatric, fatigue, sleep, and pain symptoms of patients with post-COVID-19 conditions [2,4,23–25]. Paradoxically, the proportion of bacterial infection in COVID-19 patients in the HBOT group surpassed that of the non-HBOT group in the present study. It is possible that our sample size was so small that it led to a biased conclusion. In addition, the risk of transmission of droplets and aerosols during the HBOT procedure cannot be ignored. Preventing the spread of pathogens should be prioritized when we are combatting respiratory infections treated with HBOT [26].

Thus, our study has certain limitations. Firstly, our research was conducted with a small sample size in a retrospective observation from North China, which may affect the generalizability of this work. It would be better to conduct extensive research among a larger population from multiple centers to reveal relevant findings. Secondly, our research was a subtle description study providing limited evidence of the co-occurring or secondary infections in COVID-19 patients with HBOT, thus, the results should be interpreted with caution.

Conclusions

The profile of co-occurring or secondary infections in COVID-19 patients treated with HBOT from North China was retrospectively described for the first time in the single-center cohort. Patients hospitalized with COVID-19 had a higher incidence of co-occurring or secondary infections. It is worth noting that MDRO infections were detected in the COVID-19 population. Appropriate prescription and optimized application of antibacterials cannot be overemphasized. The findings may improve co-occurring or secondary infection management of patients with respiratory infections treated with HBOT, including but not limited to COVID-19, in future clinical practice.

Acknowledgments

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Data availability

The data analyzed in this study are available from the corresponding author upon reasonable request.

Ethical approval

The Research Ethics Committee of Shanxi Bethune Hospital approved the study protocol and waived the requirement for informed consent from the participants (YXLL-2023-254).

Authors' contributions

Study initiation: PY, JZ, QM, PW; protocol design: PY; laboratory data collection and interpreting antimicrobial susceptibility test results: HW, ZL; data retrieval: SW, ZX; data curation and refinement: YZ, QN; statistical analysis: JZ; manuscript writing: PY; manuscript editing: BZ, ZW; funding support, QM, PW.

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