Volume 18 - Number 3-4 September 2023

Multidisciplinary Respiratory Medicine

Official Journal of SIPI (Società Italiana di Pneumologia Interdisciplinare)
Rivista ufficiale di SIPI (Società Italiana di Pneumologia Interdisciplinare)

Impact Factor 2022 2.3
Cite score 2022 5.0
SJR value 2022 0.685
SNIP 2022 0.963

Abstracted/Indexed in: PubMed, PubMed Central, Embase, ESCI, Academic Search, DOAJ, EBSCO, Google Scholar, OCLC, SCImago, Summon and SCOPUS

pagepress

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Rivista ufficiale di SIPI (Società Italiana di Pneumologia Interdisciplinare)
www.sipimrm.it

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PRODUCTION ONLINE VERSION

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PRODUCTION PRINT VERSION AND ADVERTISING

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SUBSCRIPTION INFORMATION

Annual subscription rate for the print version (3 issues plus eventual supplements) € 90.00.
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ISSN 1828-695X

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ORIGINAL RESEARCH ARTICLE

OPEN ACCESS

Impact of viral co-infection on clinical outcomes and mortality of COVID-19 patients: a study from Saudi Arabia

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ABSTRACT

Background: In COVID-19 patients undetected co-infections may have severe clinical implications associated with prolonged hospitalization, ICU admission, and mortality. Therefore, we aimed to investigate the impact of viral co-infections on the outcomes of hospitalized patients with COVID-19 in a large tertiary Saudi Arabian Hospital.
Methods: A total of 178 adult patients with confirmed SARS-CoV-2 who were hospitalized at the Armed Forces Hospital Southern Region (AFHSR), Saudi Arabia, from March 1st to June 30th 2022, were enrolled. Real-time PCR for the detection of viral co-infections was carried out. Cases (SARS-CoV-2 with viral coinfections) and control (SARS-CoV-2 mono-infection) groups were compared.
Results: 12/178 (7%) of enrolled COVID-19 patients had viral coinfections. 82/178 (46%) of patients were males. 58% of patients had comorbidities. During the study period, 4/12 (33%) and 21/166 (13%) cases and control patients died, p=0.047, respectively. Duration of hospitalization was the only significant independent factor associated with SARS-CoV-2 coinfections, OR 1.140, 95% CI 1.020-1.274, p=0.021.
Conclusions: The findings of this study from a large tertiary Saudi Arabian Center revealed a prevalence of 7% for SARS-CoV-2 viral coinfections. SARS-CoV-2 coinfected patients had a significantly prolonged duration of hospitalization and higher mortality than those with SARS-CoV-2 alone. Future studies are needed

Key words: COVID-19; virus; coinfection; outcomes; clinical; mortality; hospitalization; impact.

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Contributions: All the authors made a substantive intellectual contribution, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Ethics approval and consent to participate: Ethical approval was obtained from the institutional review board of the AFHSR (approval no; AFHSRMREC/2022/PULMONOLOGY-INTERANL MEDICINE/603).

Availability of data and material: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest: The authors declare no competing interests.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Introduction

Beyond SARS-CoV-2 pathogenesis, the incidence of infections of other respiratory viruses along with COVID-19 has been observed in different studies worldwide [1]. The impact of viral coinfection on COVID-19 patients is not fully understood but pathologically, respiratory viruses can damage the airway epithelium, decrease mucociliary clearance, and trigger immune system disorders [2]. Therefore, in COVID-19 patients undetected co-infections may have severe clinical implications associated with increased hospitalization, varied treatment approaches and mortality [1,3,4]. Earlier studies have shown that common viral co-infections reported in COVID-19 patients include Influenza viruses, respiratory syncytial virus (RSV), and adenovirus [5].

The novelty of SARS-CoV-2 and the complexity of the profound etiology of co-infection highlight the importance of consideration of associated comorbidities. COVID-19 patients with underlying comorbidities such as diabetes mellitus, hypertension, chronic kidney disease, and heart failure have been associated with COVID-19 disease severity [6]. Moreover, comorbidities were linked with increased hospitalization, prolonged stay in the intensive care unit (ICU), and mortality [7].

Studies found contradictory results concerning the impact of coinfection on the outcomes of COVID-19; one study reported that the prevalence of bacterial infection was nearly 7%, and most secondary infections were associated with compromised patients [8]. On the other hand, a recent meta-analysis found that influenza viral coinfection did not significantly increase the risk of in-hospital mortality, while it significantly reduced the risk of critical illness [9]. Moreover, studies of COVID-19 coinfections from Saudi Arabia have shown different results. Alosaimi *et al.* [4] had shown evidence of co-infection in 71% of COVID-19 patients, and viral coinfections were associated with increased ICU admission and higher mortality compared to bacterial coinfections. On the other hand, Alhoufie *et al.* [10] revealed that seropositivity for influenza A and B and parainfluenza-2 occurred only in 4.2% of COVID-19 patients. All coinfection cases were mild and misdiagnosed during the care period in the hospital. Therefore, in the current study, we aimed to investigate clinical characteristics, impact of comorbidities and the outcomes of respiratory virus co-infections in hospitalized people with COVID-19 in a large tertiary Saudi Arabian Hospital.

Materials and Methods

Study population

This was a single-center, retrospective case-control study, including a total of 178 adults (≥14 years) patients with confirmed SARS-CoV-2 who were hospitalized at the Armed Forces Hospital Southern Region (AFHSR), Khamis Mushayt, Saudi Arabia, during the late-stage of the pandemic from March 1st to June 30th 2022. Testing for additional respiratory viruses was done using RT-PCR for influenza virus (A or B) and respiratory syncytial virus (RSV), at the discretion of the treating clinician.

Subjects were included in the co-infected group if they had positive test results registered for influenza virus or RSV, and they were labeled as the "cases' group". Patients were included in the SARS-CoV-2 mono-infected group if they had a negative test result registered for influenza virus or RSV, and they were labeled as the "control group". Demographic and clinical data and laboratory results were collected at the time of hospital admission from the patients' medical records.

Comorbidities were collected individually as well as summarized as an overall comorbidity count, with each comorbidity having the same weight. Included comorbidities were chronic cardiac disease, chronic pulmonary disease, chronic kidney disease, chronic liver disease, diabetes mellitus (type 1 or 2), chronic neurological disease, connective tissue/rheumatological disease, malignant neoplasm, dementia, and HIV/AIDS.

Comparison between the cases and control groups was carried out with regard to demographic, clinical, laboratory data, duration of hospitalization, location of care (ICU or non-ICU), and outcomes.

Real time PCR for detection of SARS-CoV-2 and viral co-infections

The Xpert Xpress CoV-2/Flu/RSV *plus* test is an automated *in vitro* diagnostic test for the simultaneous qualitative detection and differentiation of RNA from SARS-CoV-2, Flu A, Flu B, and RSV (Cepheid, Sunnyvale, CA, USA). The Xpert Xpress CoV-2/Flu/RSV *plus* test is performed on GeneXpert Instrument Systems (Dx and Infinity Systems). The primers and probes in the Xpert Xpress CoV-2/Flu/RSV *plus* test are designed to amplify and detect unique sequences in the following: nucleocapsid (N) and envelope (E) and RNA-dependent RNA polymerase (RdRP) genes of the SARS-CoV-2 virus genome, influenza A matrix (M), influenza A basic polymerase (PB2), influenza A acidic protein (PA), influenza B matrix (M), influenza B nonstructural protein (NS), and the RSV A and RSV B nucleocapsid.

A nasopharyngeal swab specimen is collected and placed into a transport tube containing 3 mL of viral transport medium. The specimen is briefly mixed by rapidly inverting the collection tube 5 times; 300 uL of the sample is transferred to the sample chamber of the Xpert Xpress SARS-CoV-2/Flu/RSV cartridge (Cepheid). The GeneXpert cartridge is loaded onto the GeneXpert Instrument System platform, which performs hands-off, automated sample processing, and real-time RT-PCR for the detection of viral RNA.

Ethical considerations

Ethical approval was obtained from the institutional review board of the AFHSR (approval no; AFHSRMREC/2022/PULMONOLOGY-INTERNAL MEDICINE/603). The study participants were fully informed about the study procedures and informed consent was obtained from the study participants.

Statistical analysis

Significance testing for continuous normally distributed variables was done using the paired *t*-test for 2 groups and a one-way ANOVA for viral co-infections, respectively. Significance testing for continuous non-normally distributed values was done using the Mann Whitney-U test for 2 groups and the Kruskal Wallis test for comparing the viral co-infections, respectively.

A multivariable regression analysis was performed to analyze the effect of viral co-infection independent of other variables. The confounders used were age, gender, presence or absence of comorbidities, duration of hospitalization, location of care, laboratory and radiological findings, and the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) 4C mortality score. A p of 0.05 or less was considered to indicate statistical significance. Statistical analysis was performed using the Statistical Package for Social Science (SPSS) Software (version 24).

Results

Demographic and clinical characteristics

Our results showed that 12/178 (7%) of enrolled COVID-19 patients had viral coinfections. Out of these, 8(67%), 2(16.5%), and 2(16.5%), had influenza A, influenza B, and RSV, respectively. Eighty-two out of 178 (46%) patients were males. The patients' average age was 65 years, with a range of 15-109 years. There were no significant differences between the cases and control groups with regard to age, gender, vital signs [temperature, respiratory rate (RR), and oxygen saturation (O_2 sat)]. Cases had lower values Glasgow Coma Scale (GCS) than control subjects (p=0.036) (Table 1).

Comorbidities

One hundred and three patients out of 178 (58%) had comorbidities. These comorbidities included diabetes mellitus (72/178, 40%), hypertension (78/178, 44 %), chronic cardiac (73/178, 41%), chronic respiratory (20/178, 11%), chronic renal (38/178, 21%), and chronic neurological (39/178, 22%) diseases, respectively. Ninety-one (161/178) percent of patients had up to 3 morbidities, while 9% (17/178) had 4 to 6 comorbidities. Characteristically, there was neither a significant difference between cases and controls with regard to the presence or absence of comorbidities nor the number of comorbidities. Also, there was no significant difference between cases and controls with regard to any single comorbidity (Table 1).

Laboratory findings

There were significant differences between the cases and control groups with regard to blood urea nitrogen (BUN), C-reactive protein (CRP), and lactate dehydrogenase (LDH), p=0.036, <0.001, and 0.036, respectively. There were no significant differences between the 2 groups with regard to lymphopenia and D-dimer levels (Table 2).

Outcomes

There was a significant difference between the cases and control groups with regard to days of hospitalization, 12.09±20.29 days *versus* 6.29±5.13 days, p=0.015, respectively. Sixteen percent (29/178) of enrolled patients needed intensive care unit (ICU) admission, with no significant difference between cases (25%) and controls (16%) with regard to ICU admission, p=0.401, respectively. During the study period, 4/12(33%) and 21/166(13%) cases and control patients died, p=0.047, respectively. Among the cases who died, all of them had influenza A coinfection and 3 out of 4 (75%) were admitted to the ICU. There was no significant difference between the cases and control groups with regard to the ISARIC 4C mortality score, p=0.227 (Table 3).

Logistic regression analysis

The confounders of age, gender, presence or absence of comorbidities, duration of hospitalization, location of care (ICU versus non-ICU), lymphopenia, LDH, D-dimer, the 4C mortality score, and outcome (survived versus died) were pooled into a multivariable regression analysis to analyze the effect of viral co-infection

Table 1. Demographic and clinical characteristics of the study groups.

Baseline variable	All patients (n=178)	Control group (n=166, 93%)	Cases group (n=12, 7%)	p
Age (years)				0.750
Mean±SD	65.1±23.31	65.6±23.49	59.5±21.43	
Median	69.0	69.0	69.0	
Range	15-109	15-109	31-95	
Gender				0.140
Females	96 (54%)	92 (55%)	4 (33%)	
Males	82 (46%)	74 (45%)	8 (67%)	
Temperature (°C)				0.223
Mean ±SD	37.2±0.8	37.11±0.82	36.9 ± 5.3	
Median (IQR)	37.1 (0.7)	37.15 (0.7)	36.8 (0.5)	
Respiratory rate (Breathes/minute)				0.055
<20	102 (58%)	98(59%)	4(33%)	
20-29	63 (35%)	55(33%)	8 (67%)	
>30	13 (7%)	13(8%)	0 (0%)	
O_2 saturation (%)				0.540
<92%	110 (62%)	104 (63%)	6 (50%)	
>92%	68 (38%)	62 (37%)	6 (50%)	
GCS				0.036
<15	24 (13%)	20 (12%)	4 (33%)	
15	154 (87%)	146 (88%)	8 (67%)	
Comorbidities				0.973
No	75 (42%)	70 (42%)	5 (42%)	
Yes	103 (58%)	96 (58%)	7 (58%)	
No. of comorbidities				0.846
Median (IQR)	2.0 (3.0)	2.0 (3.0)	1.0 (3.0)	
No. of comorbidities				0.883
0-3	161 (91%)	150 (90%)	11 (92%)	
4-6	17 (9%)	16 (10%)	1 (8 %)	

IQR, interquartile ratio; O_2, oxygen; GCS, Glasgow Coma Scale.

independent of these variables. Duration of hospitalization was the only significant independent factor associated with SARS-CoV-2 coinfections, OR 1.140, 95% CI 1.020-1.274, p=0.021 (Table 4).

Discussion

In this study, we investigated the presence of viral co-infections in COVID-19 patients and analyzed their clinical characteristics and their impacts on outcomes.

Our results have shown that 7% of enrolled COVID-19 patients had viral coinfections. In their meta-analysis, Musuuza *et al.* [11] found that the rate of viral coinfections was 10%, in which influenza virus and RSV were the typical pathogens. However, in the meta-analysis by Dadashi *et al.* [12] a total of 11 studies (n=3,070 patients) were pooled to identify the prevalence of influenza virus coinfection in COVID-19 patients which was 0.8%. These similarities and differences could be attributed to different population characteristics, different COVID-19 global distributions, and seasonal influenza variations, and methods of viral testing. Earlier in the pandemic, quarantine, social distancing, self-isolation and the wearing of face coverings have reduced transmission of SARS-CoV-2. These countermeasures have also reduced the transmission and associated disease burden of other endemic respiratory viruses, such as influenza and RSV [13,14]. However, as these countermeasures are less stringently implemented (at the time of the current study, 2022), it is plausible we will see an increase in SARS-CoV-2 viral coinfections [4]. This may explain our findings of a 7% prevalence of viral coinfections among our COVID-19 cohorts.

Our data revealed that 84% of COVID-19 viral coinfections were due to influenza A and B. Influenza has been the predominant cause of severe seasonal respiratory viral disease for decades [15]. Risk factors for severe viral pneumonia are similar in SARS-CoV-2 and influenza [12,16]. Whilst RSV mainly causes bronchiolitis in children, it can cause severe viral pneumonia in the elderly and immunocompromised, both influenza virus and SARS-CoV-2 damage the epithelial cells and cause inflammation [17,18]. Thus, the seasonal influenza virus can cause severe disease leading to ICU admission, the need for mechanical ventilation (MV) and even death [4,18]. Despite that 16% of our enrolled patients needed ICU admission, there was no significant difference between cases and controls with regard to ICU admission.

Table 2. Laboratory findings of the study groups.

Baseline variable	All patients (n=178)	Control group (n=166, 93%)	Cases group (n=12, 7%)	p
Lymphopenia (x10^9/L)	1.08 (1.07)	1.09 (1.04)	1.05 (1.36)	0.599
BUN (mg/dl)				0.036
<7	94 (53%)	91 (55%)	3 (25%)	
7-14	48 (27%)	41 (25%)	7 (58%)	
>14	36 (20%)	34 (20%)	2 (17%)	
CRP				<0.001
<50	76 (43%)	76 (46%)	0 (25%)	
51-99	42 (23%)	33 (20%)	9 (75%)	
>100	60 (34%)	57 (34%)	3 (25%)	
D-dimer (mg/L FEU)	2.1 (2.68)	1.94 (2.71)	4.0 (5.0)	0.143
LDH (IU/L)				0.036
253.0 (106.0)	255.0 (105.25)	295.0 (81.0)		

BUN, blood urea nitrogen; CRP, C-reactive protein; LDH, lactate dehydrogenase.

Table 3. Outcomes of the study groups.

Variable	All patients (n=178)	Control group (n=166, 93%)	Cases group (n=12, 7%)	p
Hospitalization days	6.78±7.64	6.29±5.13	12.09±20.29	0.015
Location				0.401
ICU	29 (16%)	26 (16%)	3 (25%)	
Non-ICU	149 (84%)	140 (84%)	9 (75 %)	
4C score				0.227
0-3	65 (36%)	63 (38%)	2 (17%)	
4-8	35 (20%)	31 (19%)	4 (33%)	
9-14	64 (36%)	60 (36%)	4 (33%)	
≥15	14 (8%)	12 (7%)	2 (17%)	
4C score				0.199
<9	165 (93%)	155 (93%)	10 (83%)	
≥9	13 (7%)	11 (7%)	2 (17%)	
Outcome				0.047
Survived	153 (86%)	145 (87%)	8 (67%)	
Died	25 (14%)	21 (13%)	4 (33%)	

ICU, intensive care unit; 4C score, International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) 4C mortality score.

Table 4. Multivariable logistic regression analysis.

Variable	Odds ratio	95% CI	p
Age	0.967	0.923-1.013	0.152
Gender (male)	0.720	0.129-4.037	0.709
Comorbidities			
No	1	-	-
Yes	0.077	0.002-3.090	0.174
Location			
Non-ICU	1	-	-
ICU	2.795	0.235-33.251	0.416
Lymphopenia	1.160	0.952-1.414	0.142
LDH	0.999	0.999-1.002	0.766
D-dimer	1.086	0.991-1.191	0.079
Hospitalization days	1.140	1.020-1.274	0.021
Outcome			
Survived	1	-	-
Died	0.113	0.009-1.391	0.089
4C score	1.865	0.395-7.198	0.481

ICU, intensive care unit; 4C score, International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) 4C mortality score.

The novelty of SARS-CoV-2 and the complexity of the profound etiology of viral and bacterial coinfections urged clinicians to consider comorbidities. In their systematic review and meta-analysis of 42 studies and 423,117 patients, Dessie and Zewotir [19] concluded that clinical risk factors for a fatal outcome associated with coronavirus are those chronic comorbidities, complications, and demographic variables including acute kidney injury, COPD, diabetes, hypertension, CVD, cancer, increased D-dimer, male gender, older age, current smoker, and obesity [19]. Despite that 58% of our enrolled patients had at least one comorbidity, we could not find a significant difference between cases and controls with regard to the presence or absence of comorbidities or their number. This could be partially explained by the relatively low number of the study cohort.

Given the fact that some demographic data, laboratory markers, and radiological findings are of crucial importance in patients with COVID-19, Izcovich *et al*. [20] had conducted their systematic review to identify those prognostic factors that may be used in decision-making related to the care of patients infected with COVID-19. They found that 49 variables provide valuable prognostic information on mortality and/or severe disease in patients with COVID-19 infectious disease [20]. In concordance with these data, we observed that patients with SARS-Co-V2 viral coinfections had significantly higher BUN, and LDH, in comparison to those with SARS-Co-V2 alone. Interestingly, the average age of the current study population was 65 years, with some patients aged up to 109 years. Identified prognostic factors can help clinicians and policymakers in tailoring management strategies for patients with COVID-19 and improving their outcomes [4,20].

Our data revealed that patients with SARS-Co-V2 viral coinfections had a significantly prolonged duration of hospitalization and higher mortality compared to those with SARS-Co-V2 alone. One-third of SARS-Co-V2 coinfected with influenza A died during the study period. Our results emphasize the importance of screening of viral coinfections in patients with COVID-19. SARS-Co-V2 coinfected patients are more likely to have severe disease, prolonged hospitalization, utilization of health care resources, ICU admission, and more importantly higher mortality. With this regard, our results are in agreement with previous reports [3,4,11,18]. Drake and colleagues [21] found 138 influenza-co-infected patients, including children, in which a prolonged duration of hospital admission was found, although this was not corrected for the likelihood of being tested. Alosaimi and coworkers [4] identified 30 co-infected patients out of 48 hospitalized (14 ICU) SARS-CoV-2 positive patients and found that influenza co-infection was associated with mortality.

The current study highlights an important notification. During the SARS-CoV-2 pandemic, especially in its late stages, focusing on the detection and management of this novel virus may lead to underreporting of other pathogens (like influenza) that could be the etiological agents for severe lung disease. Taking into consideration the natural life cycles of viruses; although respiratory viral co-infections were uncommon during the first two years of the COVID-19 pandemic, as public health guidance changes and social mixing increases, co-circulation of additional respiratory viruses will also increase leading to more co-infections [3,4,11,18,21,22].

The current study emphasizes the importance of preventive measures to reduce the disease burden associated with these viral coinfections, in particular influenza vaccination. The adoption of more widespread testing will identify patients in whom different therapeutic strategies may be more effective and would facilitate the identification of hospital inpatients at high risk of deterioration and death [3,21,22].

Our study has some strength points. First, data are representative of many patients referred to a large tertiary Saudi Hospital. Second, data were collected from in-patients, where close monitoring and easier follow-up could be implemented [10]. On the other hand, our study has some limitations. First, the inherited limitation of being a retrospective analysis. Second, a single-center experience was encountered. Third, the number of cases is relatively low for the number of controls. Lastly, influenza vaccination history was not clear for most of our patients. Further prospective studies are needed to clarify the SARS-Co-V2 viral coinfections.

Conclusion

The findings of this study from a large tertiary Saudi Arabian Center revealed a prevalence of 7% for SARS-CoV-2 viral coinfections. SARS-CoV-2 coinfected patients had a significantly prolonged duration of hospitalization and higher mortality than those with SARS-CoV2 alone. Future studies are needed.

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Received for publication: 27 March 2023. Accepted for publication: 2 May 2023.

Multidisciplinary Respiratory Medicine 2023; 18:915
doi:10.4081/mrm.2023.915

Multidisciplinary Respiratory Medicine 2022; volume 17:875

ORIGINAL RESEARCH ARTICLE

Long-lasting dyspnoea in patients otherwise clinically and radiologically recovered from COVID pneumonia: a probe for checking persisting disorders in capillary lung volume as a cause

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ABSTRACT

Background: During SARS-CoV-2 infection, diffuse alveolar damage and pulmonary microvascular abnormalities are critical events that result in gas exchange disorders of varying severity and duration. The only measure of carbon monoxide (CO) diffusing capacity (DL_{CO}) is unable to distinguish the alveolar from the vascular side of present and residual diffusive abnormalities, and measure of nitric oxide (NO) diffusing capacity (DL_{NO}) is also recommended. Dyspnoea, despite being understudied, persists in a significant proportion of patients for several weeks after hospital discharge. The goal of this study was to look into the underlying cause of long-term dyspnoea in patients who were "clinically and radiologically recovered" from COVID pneumonia by assessing DL_{CO} and DL_{NO} at the same time.
Methods: Patients of both genders, aged ≥18 years, who had a CT scan showing complete resolution of COVID-related parenchymal lesions were recruited consecutively. Spirometrical volumes, blood haemoglobin, SpO_2, DL_{CO}, DL_{NO} and capillary blood volume (Vc) were measured. Data from patients without dyspnoea (group A) and from patients still claiming dyspnoea after 12-16 weeks from their hospital discharge (group B) were statistically compared.
Results: Forty patients were recruited: 19 in group A and 21 in group B. Groups were comparable for their general characteristics and spirometrical volumes, that were in the normal range. Mean values for DL_{CO}, DL_{NO} and Vc were significantly and substantially lower than predicted only in patients of group B ($p<0.011$; $p<0.0036$; $p<0.02$; $p<0.001$, respectively). The DL_{NO}/ DL_{CO} ratio was higher in group B ($p<0.001$) and inversely correlated to Vc values (-0.3636).
Conclusions: The single-breath, simultaneous measurement of DL_{CO}, DL_{NO}, and Vc demonstrated that problems with blood gas exchange can persist even after parenchymal lesions have healed completely. Regardless of the normality of spirometric volumes, there was a significant reduction in lung capillary blood volume. In these patients, the cause of long-term dyspnoea may be related to hidden abnormalities in the vascular side of diffusive function. In the near future, novel therapeutic approaches against residual and symptomatic signs of long-COVID are possible.

Key words: COVID-19; vascular effects; lung perfusion, capillary blood volume (Vc); carbon monoxide diffusing capacity (DL_{CO}); nitric oxide diffusing capacity (DL_{NO}).

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Contributions: RWD planned the study and wrote the manuscript; PT, provided critical feedback and contributed to the final version of the manuscript; MP carried out all statistical calculations. All authors approved the final version of the manuscript.

Conflict of interest: All authors declare no conflict of interest in the present investigation. RWD is Associate Editor of *Multidisciplinary Respiratory Medicine.*

Ethics approval and consent to participate: The study was approved by the Ethical and Scientific Commission of the National Centre for Respiratory Pharmacoeconomics and Pharmacoepidemiology during the session of May 2nd, 2021. At recruitment, all subjects gave their informed consent also to the anonymous use of their own data for research purposes.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Introduction

COVID-19 caused by SARS-CoV-2 infection has an extremely variable natural history, ranging from asymptomatic or mild clinical picture involving only the upper airways to diffuse interstitial pneumonia with hypoxemic respiratory failure (and/or fatal multiorgan failure), especially in fragile or predisposed individuals [1-7].

The effects of two major biologic cascades dominate the field: the diffuse damage at alveolar level (including injury to the alveolar epithelial cells, hyaline membrane formation, fibrin deposition, hyperplasia of type II pneumocytes) [8], and pulmonary congestion, with microvascular thrombosis and occlusion [9]. The local high concentration of cytokines and chemokines that contribute to the recruitment of inflammatory cells, combined with the production of IgM-mediated immunocomplexes, can contribute to platelets and tissue factors activation, further leading to coagulation and micro-thrombosis, as seen in COVID-19 patients with acute respiratory failure (RF) [2]. All of these structural changes can essentially support the occurrence of a significant disruption in alveolar-blood gas exchange [10].

Though understudied in clinical practice, long-term dyspnoea of varying extent and duration is claimed by a not insignificant proportion of patients who were incorrectly defined as "clinically recovered" from COVID-19 pneumonia several weeks before [11].

In terms of lung function abnormalities, in addition to a variable restrictive pattern of lung volumes, a mild reduction in diffusing capacity for carbon monoxide (DL_{CO}) was the only lung function limitation reported as occurring in approximately 30% of patients for several weeks after hospital discharge [12-15].

Unfortunately, due to the slow binding of CO with intracapillary haemoglobin (Hb), the current assessment of DL_{CO} is insufficient to distinguish abnormalities in the alveolar membrane diffusing conductance (DM) from those involving the vascular side of diffusion, such as capillary blood volume in the lung (Vc). For these reasons, DL_{NO} evaluation is also recommended [16-18]. Furthermore, it has recently been demonstrated that changes in gas transport can be observed even in subjects who have mild COVID-19 pneumonia with no or minimal persisting CT abnormalities [19].

A non-invasive, single-breath technology that allows rapid differentiation between DM and Vc disorders is now available for clinical use [20-21], providing an excellent opportunity to investigate deeper into the unexplained cause of persistent dyspnoea in long-COVID patients.

The purpose of this study was to look into the cause of dyspnoea that lasted several weeks in patients who were otherwise considered "clinically and radiologically recovered" from COVID pneumonia.

Methods

Patients of both genders aged ≥18 years who had been previously regarded as "clinically recovered" for 12-16 weeks after discharge for COVID pneumonia (hospital admission over the previous six months) and provided with a recent (i.e., within the last two weeks before recruitment) CT scan showing a complete resolution of any COVID-related parenchymal lesions were recruited consecutively between September 1, 2021 and March 15, 2022, after their informed consent.

Exclusion criteria were: current and former-smokers; age <18 years; the presence of major comorbidities affecting the diffusion measurements (such as: anaemia (blood Hb <12g/L); heart failure; COPD; lung fibrosis; vasculitis; liver and renal failure; diabetes); the persistence of COVID-related parenchymal abnormalities; the presence of physical limitations and/or cognitive impairment enabling procedures for lung function tests; the refusal of the informed consent.

Further to age, gender, BMI, and other possible comorbidities not interfering with diffusion measures, the following parameters were collected in all patients:

- Hb (blood haemoglobin, in g/L);
- SpO_2 (O_2 saturation, in %);
- VC (vital capacity) and FEV_1 (forced expiratory volume in 1 sec), both reported as % predicted);
- DL_{co} (diffusing capacity for carbon oxide); Kco (DL_{CO} /VA – alveolar volume); DL_{NO} (diffusion capacity for nitric oxide); Kno (DL_{NO} /VA – alveolar volume); Vc (capillary blood volume), and DL_{NO} / DL_{CO}). All parameters were reported as % predicted.

Spirometrical parameters were obtained by means of a Plethysmography Platinum DX Elite (MedGraphics, Saint Paul, MN, USA). Diffusion parameters were measured by means of the "Stand-Alone" Hypair Compact System (MGC Diagnostics International, Sorinnes, Belgium) that allows the simultaneous assessment of DM and Vc as a function of the standard single-breath method. This method is based on the principle by Roughton and Forster [22] of two reactions of THETA fractions: one for CO, and the other one for NO, according to the values fixed in the ERS/ATS Task-Force 2017 [23], during the usual single breath manoeuvres. Due to the use of an electrochemical analyser for NO, the usual DL_{CO} measure apnoea time duration of 10 sec, is reduced for DL_{NO} around 5 sec. Two gas mixtures are required for these measures: i) helium (He) 14%; CO 0.280%; oxygen (O_2) 18–21, and nitrogen (N_2), and ii) nitric oxide in nitrogen (NO in N_2) 400 ppm. According to standard procedures, measure of DL_{CO} and DL_{NO} required breath-hold times of 10 and 5 sec, respectively.

Current dyspnoea was checked and graded in each patient according to the modified British Medical Research Council (mMRC) dyspnoea score [24], and its duration after discharge was also reported.

The whole sample was then divided in two groups of patients to compare: i) those who did not report any significant dyspnoea (Dys-), and ii) those still claiming dyspnoea (DYS+).

Statistics

Continuous data were presented as means and standard deviation (SD), while sex as absolute and relative frequencies. Differences in all variables collected in the two groups were tested by *t*-test for continuous data and by Fisher exact test for categorical data; $p<0.05$ was accepted for statistical significance. Furthermore, correlation analysis was performed to explore the linear association between all the lung function parameters in the whole sample.

All statistical calculations were carried out by means of STATA (StataCorp 2017. Stata Statistical Software: Release 15; StataCorp LLC, College Station, TX, USA); $p<0.05$ was assumed as the limit of statistical significance.

Ethics statement

At recruitment, all subjects gave their informed consent also to the anonymous use of their own data for research purposes. The study was approved by the Ethical and Scientific Commission of the National Centre for Respiratory Pharmacoeconomics and Pharmacoepidemiology during the session of May 2nd, 2021.

Results

General data

The whole sample consisted of 40 patients: 21 patients still reporting persisting dyspnoea at different extent for 12-16 weeks after their discharge, and 19 without any significant dyspnoea over the same period. General data are reported in Table 1.

Patients of the two groups were well matched for all general variables considered, including comorbidities that were evenly distributed in the two groups, both in terms of their frequency and type. Obviously, the dyspnoea duration after discharge and the current dyspnoea score proved significantly much higher in patients of group B.

Specific parameters in the whole sample

Mean blood Hb values and mean values for all lung function parameters assessed in the whole sample are reported in Table 2.

The whole sample of patients showed mean basal values for Hb, SpO_2, VC and FEV_1 in their predicted normal range. DL_{CO} and DL_{NO} mean values were slightly lower than predicted while only mean Vc values were dramatically reduced than predicted and proved to be significantly and negatively related to the values for the DL_{NO}/DL_{CO} ratio (-0.3636).

Specific parameters in the two groups

Mean values for all variables obtained in the two groups of patients are also reported in Table 2 together with the results of the corresponding statistical comparisons.

Patients of groups A and B had comparable mean basal values for blood Hb and O_2 saturation. Mean spirometrical lung volumes were in their normal range and comparable in both groups regardless of whether reporting dyspnoea or not. In particular, two patients in group A and three patients in group B had CV values lower than predicted (72% and 63% in group A, and 73%, 65%, and 63% in group B, respectively). Only one patient in group A and two patients in group B had FEV_1 values lower that predicted (68% in group A, and 73% and 68% in group B, respectively).

Nevertheless, patients in group A and B were significantly different in terms of mean values for all parameters related to CO and NO diffusion. Mean values for DL_{CO}, K_{CO}, DL_{NO}, K_{NO}, and Vc were significantly lower than predicted only in patients of group B, such as in those still claiming long-lasting dyspnoea ($p<0.011$; $p<0.0036$; $p<0.02$; $p<0.038$; $p<0.001$, respectively), while the DL_{NO}/DL_{CO} ratio was significantly higher ($p<0.001$). Moreover, three and four patients in group A, and fourteen and eleven patients in group B showed DL_{CO} and DL_{NO} absolute values lower than predicted, respectively (such as <80%). To underline that mean values for Vc proved dramatically lower than predicted in patients of group B (Table 2).

Table 1. General characteristics of the whole sample, together with those of the two groups, with corresponding statistical comparisons (means ±SD, and statistical significance). Comorbidities are reported as relative frequency.

	Whole sample	Group A dyspnoea	Group B dyspnoea +	p
n	40	19	21	
Males/females	17/23	9/10	8/13	0.39
Age (y)	49.3±19.3	48.4 ± 16.7	48.9 ± 20.6	0.92
BMI	24.9±4.6	24.7 ± 4.1	24.3 ± 4.9	0.86
Comorbidities				
mild hypertension	6		3	3
thyroiditis	1		1	-
atopy	2		1	1
Dyspnoea duration after discharge (weeks)	5.3±10.7	1.1±0.4	12.7±3.1	0.001
Dyspnoea score	0.9±1.3		0.1±0.1	1.7 ± 0.4 0.001

Table 2. Blood haemoglobin and lung function parameters in the whole sample and in two groups of patients, together with corresponding statistical comparisons.

	Whole sample	Dyspnoea -	Dyspnoea +	p
Hb (g/L)	14.11±0.1	14.06 ± 0.4	14.14 ± 0.5	0.59
SpO_2 (%)	97.2±1.8	97.8 ± 1.1	96.7 ± 1.6	0.77
VC (% predicted)	99.1±16.3	97.05 ± 12.1	99.14 ± 20.9	0.71
FEV_1 (% predicted)	96.4±15.1	95.79 ± 11.5	96.57± 17.6	0.87
DL_{CO} (% predicted)	83.7±16.9	90.5 ± 16.5	76.9 ± 15.6	0.011
K_{CO} (% predicted)	89.1±11.6	94.3 ± 12.8	83.5 ± 9.1	0.0036
DL_{NO} (% predicted)	82.3±16.9	91.7±14.0	77.9±15.9	0.022
KNO (% predicted)	96.1±11.5	99.7 ± 11.8	92.0 ± 10.9	0.038
Vc (% predicted)	56.2±13.1	62.5 ± 12.8	49.6 ± 10.2	0.001
DL_{NO}/DL_{CO} (% predicted)	116.6±9.1	111.4 ± 5.0	121.8 ± 8.6	0.001

Discussion

After more than two years of pandemic, it is now accepted that a significant proportion of patients hospitalized for COVID pneumonia may experience long-term effects after discharge [11,13,25-27]. This condition is known as "long-COVID syndrome" or "post-COVID syndrome." It is distinguished by varying lung function limitations as well as the persistence of some respiratory and extra-respiratory clinical signs [11,15,25].

Long-term dyspnoea is the most common symptom reported for several weeks, regardless of normalized lung volumes. The cause of long-term dyspnoea in these cases is still unknown. Unfortunately, the majority of cases in clinical practice remain unsolved because standard diagnostic procedures do not substantiate any cardiac involvement (the very first and practically only aspect investigated) and are generally inconclusive. In the absence of a clear cardiogenic cause, a psychological cause of persistent dyspnoea is frequently proposed. In these cases, it is generically related to the patients' anxiety, most likely due to the great fear of an impending COVID-19 relapse, but the results are equally poor. The diagnostic path usually ends here, and a time-dependent spontaneous resolution is currently anticipated.

In contrast, the cause of this long-term dyspnoea should not be overlooked in these patients. It should be looked into further based on the accumulating evidence of COVID-19-induced microangiopathy involving the lung capillary bed. This unusual disorder may be the most likely cause of the hidden gas exchange abnormalities that result in symptomatic alveolar-perfusion mismatch. In other words, these types of disorders can be perceived by post-COVID patients, and dyspnoea may be their main persistent symptom despite being defined as "clinically and morphologically recovered" [10-11].

Despite the fact that several studies only report a generic reduction in CO diffusing capacity (DL_{CO}) as the only lung function limitation in these cases [12-15], additional studies reported reduced values of the DL_{CO} -to-alveolar volume ratio (DL_{CO}/VA) in a variable proportion of COVID-19 patients, even lasting for several weeks after discharge [28-29]. Further physiological studies have recently investigated and confirmed the additive value of measuring NO diffusing capacity (DL_{NO}) in post-COVID-19 conditions [19]. The evaluation of both of these measurements (and of other related parameters) in particular helped to clarify some relevant aspects of post-COVID lung function abnormalities and to distinguish DM from Vc disorders, which can persist for several weeks after their presumed "clinical recovery" [16-19].

When considering the different affinity of NO and CO to blood haemoglobin and then the different power of DL_{NO} and DL_{CO} measurements in discriminating changes in blood volume, the hypothesis that the persistence of dyspnoea could be related to the underlying alveolar-perfusion mis-match due to the involvement of the vascular side of lung diffusion is strongly supported in these cases (Vc) [19].

For the first time, simultaneous measurements of DL_{CO}, DL_{NO}, and Vc were used in this study to investigate the potential role of hidden abnormalities in blood gas exchange in supporting long-term post-COVID dyspnoea in patients who were otherwise defined as "clinically and morphologically recovered" from COVID pneumonia. Surprisingly, the current study found that DL_{CO} and K_{CO} are significantly impaired only in patients who continue to complain of long-term dyspnoea: their values were lower than those of DL_{NO} and K_{NO}, strongly implying the presence of impaired (such as reduced) capillary blood flow within the lung in these cases. These findings, which are supported by an increased DL_{NO}/DL_{CO} ratio, point to the active role of disorders in the vascular side of pulmonary diffusion in these cases [16-19,28,29]. The evidence that Vc, such as capillary blood volume, was significantly reduced only in patients who reported dyspnoea for several weeks lends further credence to this hypothesis. This factor is critical in assessing the natural evolution of long-COVID because it is well known that the impact of symptomatic sequelae can be significant in a significant proportion of patients, even if a longitudinal improvement can be expected over the next twenty-four months from discharge [29].

The current study has some limitations: i) it is a monocentric study conducted in a small sample of post-COVID patients; ii) the original severity of COVID pneumonia was impossible to quantify because the majority of patients did not have a CT scan performed at the time of their hospital admission; and iii) the follow up period was only 12-16 weeks. Points of strength include: i) patients were carefully selected in clinical terms; ii) patients in both groups were equally investigated after a comparable period of time from their discharge from COVID pneumonia; iii) at recruitment, all patients were provided with a relatively recent CT scan showing complete resolution of any COVID-induced parenchymal abnormalities; iv) for the first time in clinical practice, the simultaneous single-breath assessment of DL_{CO}, DL_{NO}, and Vc was used to investigate both the alveolar and vascular sides of lung diffusive function; v) dyspnoea was used as a probe for discriminating the different values of these measures in still symptomatic long-COVID patients.

Conclusions

A significant proportion of patients who were deemed "recovered" from COVID pneumonia claim to have experienced long-term dyspnoea. Its cause is frequently regarded as "unexplained" and ignored, owing to the difficulty of investigating it in daily clinical practice. The occurrence and persistence of hidden abnormalities in blood gas exchange are difficult to detect and, in these cases, can elude common investigations of lung function.

Even in the presence of complete resolution of previous CT parenchymal lesions, the single-breath simultaneous assessment of DL_{CO}, DL_{NO}, and Vc Vc provided reliable information about the origin of hidden, but still present, disorders in blood gas exchange. Despite the normality of spirometric volumes, significant limitations in lung capillary blood volume were discovered.

As these measures are simple to obtain, take little time, and are inexpensive, they can be recommended for investigating all post-COVID patients who claim "unexplained" dyspnoea for long periods after discharge or their supposed "complete clinical recovery."

Finally, the main message of the present study is that the origin of "unexplained" long-lasting dyspnoea in these patients can be clarified when we pay attention to the vascular side of blood gas abnormalities.

Data from the current study, if confirmed by larger studies on similar patients, may lead to some novel and original suggestions for future therapeutic approaches against residual and symptomatic signs of long-COVID.

Acknowledgments

The authors are grateful to A. Menarini I.F.R. for the support in paper publication.

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Received for publication: 24 June 2022. Accepted for publication: 6 Septeber July 2022.

Multidisciplinary Respiratory Medicine 2022; 17:875
doi:10.4081/mrm.2022.875

Multidisciplinary Respiratory Medicine 2023; volume 18:895

ORIGINAL RESEARCH ARTICLE

OPEN ACCESS

Acute kidney injury in Coronavirus disease-19 related pneumonia in the intensive care unit: a retrospective multicenter study, Saudi Arabia

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ABSTRACT

Background: Acute kidney injury (AKI) poses a significant morbidity and mortality risk to critically ill COVID-19 patients. The aim of this study was to investigate the incidence, predictors, and outcomes of AKI in patients admitted to the intensive care unit (ICU) with critically ill COVID-19 pneumonia.
Methods: A multicenter retrospective study in Saudi Arabia of adult patients aged at least 18 years diagnosed with COVID-19 pneumonia and admitted to the intensive care unit between May 2020 and May 2021 was conducted. The occurrence of AKI and associated risk factors, the need for continous renal replacement therapy (CRRT), and the outcome were reported.
Results: The study included 340 patients admitted to the ICU with COVID-19. Their mean age was 66.7±13.4 years, ranging from 49 to 84 years, and most of them were men (63.8%). The most common concomitant diseases were hypertension (71.5%), diabetes (62.4%), IHD (37.6%), CKD (20%), heart failure (19.4%), and 81.2% suffered from ARDS. AKI occurred in 60.3% of patients, 38% were stage 1, 16.6% were stage 2, and 45.4% were stage 3. Approximately, 39% of patients required CRRT, out of which 76.2% were stage 3, which was significantly higher than the other stages ($p<0.001$). AKI patients suffered significantly from asthma and had lower levels of C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), and blood urea nitrogen (BUN) and higher creatinine levels than patients without AKI ($p<0.05$ all). The overall mortality rate was 39.4%, and the mortality rate was significantly higher in patients with AKI than in patients without AKI (48.3% *versus* 25.9%; $p<0.001$).
Conclusion: AKI is common in adults admitted to the ICU with COVID-19 and is associated with an increased risk of death. Early detection of AKI and appropriate treatment can positively impact COVID-19 outcome. CRRT is the preferred dialysis method in critically ill ICU patients with AKI.

Key words: Acute kidney injury; COVID-19 pneumonia; intensive care unit; renal replacement therapy; Saudi Arabia.

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Contributions: All authors contributed to the conception and design of the work, reviewing the literature, data acquisition, manuscript writing, and revision. SE, AA, AF wrote the first draft of the manuscript and critically reviewed and revised the manuscript. All authors read, reviewed, and approved the final text and agreed to be accountable for all aspects of the work.

Conflict of interest: The authors declare that they have no competing interests, and all authors confirm accuracy.

Ethics approval and consent to participate: Approval was obtained from Almoosa Specialist Hospital Institutional Review Board (IRB protocol number: ARC -21.03.3).

Availability of data and material: All data obtained or analyzed as part of this study are available from the corresponding author on reasonable request.

Funding: This work was not funded by any organization, institution, or individual.

Acknowledgments: We would like to thank the research centers in our hospitals.

Introduction

Coronavirus disease-19 (COVID-19) is associated with high morbidity and mortality worldwide and has overwhelmed many healthcare systems and economies. It is caused by a strain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. According to the World Health Organization (WHO), more than 590,000,000 people worldwide have been diagnosed with COVID-19 as of August 18, 2022, resulting in more than 6.4 million deaths [2]. About 30% of people infected with COVID-19 remain asymptomatic, 80% of symptomatic cases have mild and moderate disease (40% each) and 15% have severe disease requiring oxygen support. Approximately 5% develop critical COVID-19 illness characterized by pneumonia, acute respiratory failure, septic shock, and/or multiple organ dysfunction [2].

The manifestations of renal involvement in patients with COVID-19 may include proteinuria, hematuria, or acute kidney injury (AKI) and are associated with a high risk of adverse prognosis [3]. The main pathogenesis of COVID-19 associated renal disease is unknown and probably multifactorial and could be due to direct viral cytotoxic damage, the renin-angiotensin-aldosterone system (RAAS) imbalance, associated hyperinflammatory state due to re-released cytokines, microvascular injury and prothrombotic state, hypovolemia, potentially nephrotoxic agents, and nosocomial sepsis [4].

There are data on the temporal evolution of the incidence of COVID-19-associated AKI. Preliminary data suggest that AKI rates declined during the duration of the pandemic, although the reason for this evolution is unclear [5,6]. In a meta-analysis of approximately 13,000 mostly hospitalized patients, the incidence of AKI was 17 percent (range 0.5 to 80%), and about 5% of patients needed renal replacement therapy (RRT). Incidence appears to vary by geographic location and proportion of critically ill patients in each study [7].

In two large observational studies of more than 5,000 patients hospitalized with COVID-19, approximately 32 to 37 percent were found to have AKI. Out of the patients with AKI, about 50% had the mild disease (1.5- to 2-fold increase in serum creatinine) and the remainder had moderate or severe disease (more than a doubling of creatinine) [5,8]. Independent predictors of AKI included advanced age or maleness, obesity, essential hypertension, diabetes mellitus, cardiovascular disease, and low estimated glomerular filtration rate (eGFR), as well as higher interleukin-6 levels and need for mechanical ventilation or vasopressor therapy [9,10]. Continuous renal replacement therapy (CRRT) is the preferred treatment for AKI or end-stage renal disease (ESRD) in critically ill patients in the ICU, usually with hemodynamic instability, when dialysis is required (e.g., volume overload, electrolyte disturbances including hyperkalemia, acidosis, and complications of uremia) [11]. The aim of this study was to investigate the incidence, risk factors, and consequences of AKI in patients admitted to the intensive care unit with critically ill COVID-19 pneumonia.

Methods

This study was part of a larger project investigating various clinical and epidemiological aspects of COVID-19 pneumonia in Saudi Arabia. It was a retrospective, multicenter study of 340 adult patients ≥18 years of age admitted to the intensive care unit of a Saudi Almoosa Specialist Hospital-Al Ahsa, Obeid General Hospital-Hofuf, and King Khaled Hospital-Hail for confirmed COVID-19 pneumonia. This study was conducted from May 2021 to May 2022. Ethical approval was obtained from the Institutional Review Board of our hospitals (Almoosa Academic Affairs: IRB log No: ARC -21.02.02).

Inclusion criteria

Adult patients (≥18 years) with COVID-19 pneumonia and hypoxemia (positive SARS-CoV-2 real-time polymerase chain reaction (PCR) nasopharyngeal swabs or respiratory secretions) were admitted to the ICU.

Exclusion criteria

Patients with COVID-19 pneumonia who did not not fulfill the criteria of ICU admission, patients admitted to the ICU for reasons other than COVID-19 pneumonia, patients who had COVID-19 infection but were not hospitalized, and pediatric COVID-19 patients were excluded. Patients with ESRD and kidney transplant patients were also excluded.

Data collections and outcomes

All the cases were diagnosed and treated according to the Saudi Ministry of Health protocol for confirmed cases of COVID-19 infection [12].

The following data were collected (within 24 h of hospitalization): age, sex, body mass index (BMI), comorbidities (such as hypertension, asthma, type 2 diabetes, and other concomitant diseases), patient symptoms, and general and local examination findings, including vital signs. The following examination results were obtained from the electronic medical record: identification of SARS-CoV-2 virus by nasopharyngeal swab using PCR, chest radiograph (portable), oxygen saturation with a pulse oximeter, arterial blood gases, complete blood count (CBC), complete metabolic panel (serum sodium, potassium, and magnesium), serum ferritin, D-dimer, lactate dehydrogenase (LDH), C-reactive protein (CRP), renal function test (urea and creatinine), liver function test, procalcitonin, troponin, and electrocardiogram (ECG). ICU course, including length of stay, need for ventilatory support (non-invasive or invasive ventilation), need for vasopressors, prophylactic anticoagulants, antibiotics, systemic steroids, anti-interleukin 6 (tocilizumab), empiric antibiotics (per local protocol), and need for CRRT and AKI outcome and outcomes either mortality or discharge to ward. Acute kidney injury was defined as per the Kidney Disease Improving Global Outcome (KDIGO) criteria [13].

Baseline creatinine is the last serum creatinine in the last 7-365 days before admission. In patients in whom no previous serum creatinine has been measured, the serum creatinine at admission is considered the baseline creatinine. Estimated glomerular filtration rate (eGFR) is calculated based on a Modification of Diet in Renal Disease (MDRD) equation. Renal recovery is defined as a decrease in serum creatinine of more than 50%.

Statistical analysis

We used the SPSS program for Windows (IBM SPSS Statistics V 25.0, IBM Corp., Armonk, NY, USA). Mean ± SD and median and interquartile range (IQR) were used for quantitative variables, whereas frequency and percentage were used for qualitative variables. Chi-square or Fischer exact tests were used to assess differences in frequencies of qualitative variables. Independent-samples *t*-test was used to evaluate the differences in the means of the quantitative variables, whereas the Mann-Whitney U test was used for nonparametric statistics. Logistic regression analysis was used with odds ratios (OR) and 95% confidence intervals (CI) to predict factors associated with COVID-19 mortality. Only significant independent variables from the univariate analysis were included in the logistic analysis. Statistical methods were reviewed, using a significance level of $p<0.05$ (double-tailed).

Results

The study included 340 patients admitted to the ICU with COVID-19. Their mean age was 66.7±13.4 years and ranged from 49 to 84 years; most of them were men (63.8%). The most common concomitant diseases were hypertension (71.5%), diabetes (62.4%), IHD (37.6%), CKD (20%), heart failure (19.4%), and 81.2% suffered from ARDS. Associated clinical and laboratory parameters showed elevated mean HR (97.5±19.3) and RR (27.7±4.2), elevated median CRP (81 [36-136]), ferritin (964 [792-1642]), LDH (652 [452-895]), D-dimer (2.9 [2.5-3.4]), creatinine (89 [73.3-142]), and lower median PaO_2/FIO_2 ratio (62 [53-112]). The majority (91.8%) received steroid therapy and 43.5% received vasopressors. The mortality rate was 134 patients (39.4%) (Table 1). AKI occurred in 205 patients (60.3%), out of whom 78 (38%) were stage 1, 34 (16.6%) were stage 2, and 93 (45.4%) were stage 3. Eighty of 205 patients (39%) required CRRT, including 15 of 80 patients (18.8%) in stage 1, 4 patients (5%) in stage 2, and 61 patients (76.2%) in stage 3, which was significantly higher than the other stages ($p<0.001$) (Table 2). More than three-quarters (76.8%) of the patients received mechanical ventilation (MV), 14.6% received oxygen therapy with a high-flow nasal cannula (HFNC), and 4.4% received oxygen therapy with a nasal cannula (NC) (Figure 1). Patients with AKI suffered significantly from asthma, required CRRT, and had lower median CRP, ferritin, LDH, and BUN levels, and higher median creatinine levels than patients without AKI ($p<0.05$ all) (Table 3). The mortality rate was significantly higher in patients with AKI than in patients without AKI (48.3% *vs* 25.9%; $p<0.001$). Overall, 106 out of 205 patients (51.7%) with AKI were discharged; complete improvement occurred in 97 patients (47.3%), and 9 patients (4.4%) required regular dialysis because of ESRD (Figure 2).

Discussion

The pandemic COVID-19 causes numerous cases of illness and death and has overwhelmed health services and disrupted normal life and the economy. COVID-19 is characterized by a systemic inflammatory response and an increased risk of respiratory failure and AKI [1,2]. AKI is one of the most common complications of COVID-19 in hospitalized patients and is associated with a highly unfavorable outcome [5].

In this study, AKI occurred in 60.3% of patients admitted to the ICU for critical COVID-19 pneumonia. This is consistent with many studies from the United States, in which 60-80% of critical COVID-19 patients were found to have AKI [14,15]. Other studies from the USA involving COVID-19 cases admitted to the ICU, showed that more than 60% (61-78%) of them had AKI [16,17]. The incidence of AKI reached 68% in critically ill COVID-19 patients admitted to the intensive care unit. In a large cohort study in New York City [18]. Alenezi *et al*. conducted a systematic review and meta-analysis (out of 618 studies identified and reviewed, 31 studies met inclusion criteria), and the incidence of AKI was 50% in eight studies that included only COVID-19 patients admitted to the ICU (n=1,540) [19]. Our results on the incidence of AKI were lower than those of other studies. Schaubroeck *et al*. performed a multicenter cohort analysis of AKI in critically ill patients of COVID-19 in Belgium (from seven large hospitals) and found a high rate of AKI (85.1% of 1,286 cases) [20]. Lumlertgul *et al*. reported that AKI occurred in 76% of critical COVID-19 patients [21]. de Almeida *et al*. observed an increased incidence of AKI > 70%, with more than half of these patients meeting KDIGO 3 criteria within 7 days of hospitalization [22]. Our results on AKI rates in critically ill COVID-19 cases in the ICU were higher than in many

Table 1. General, clinical, laboratory and outcome characteristics of the studied patients.

Variables	n=340	(%)
Age (years)	66.7±13.4	
Sex		
Male	217	63.8
Female	123	36.2
BMI (kg/m^2)	26.9±7.0	
HTN	243	71.5
DM2	212	62.4
Asthma	19	5.6
IHD	128	37.6
CHF	66	19.4
CKD	68	20.0
HR (beats/min)	97.5±19.3	
Temperature (°C)	37.8±1.01	
RR (breaths/min)	27.7±4.2	
GCS	14.5±0.78	
PaO_2 (mmHg)	59 (50.3-65)	
CRP	81 (36-136)	
Ferritin (ng/mL)	964 (792-1642)	
LDH (IU/L)	652 (452-895)	
D-dimer	2.9 (2.5-3.4)	
HB (gm/dl)	11.4±2.2	
WBCs (cells/mm^3)	11.3 (8.2-15.4)	
Creatinine (mg/dl)	89 (73.3-142)	
BUN (mg/dl)	12.4 (9.4-18.8)	
PaO_2/FIO_2 ratio	62 (53-112)	
<300	276	81.2
>300	64	18.8
Need for vasopressors	148	43.5
ARDS	276	81.2
Mild (200-300)		
Moderate (100-200)		
Severe <100		
Steroid therapy	312	91.8
Hospital stays (days)	11 (4-18)	
Outcome		
Discharged	206	60.6
Death	134	39.4

Qualitative variables present as number and percent; quantitative variables present as mean ±SD or as median (IQR).

Table 2. Renal impairment among the studied patients.

Variables	n=340	(%)
AKI	205	60.3
AKI stage		
Stage 1	78/205	38.0
Stage 2	34/205	16.6
Stage 3	93/205	45.4
CRRT	80/205	39.0
CRRT *vs* AKI stage		
Stage 1	15/80	18.8
Stage 2	4/80	5.0
Stage 3	61/80	76.2
p	<0.001*	

Qualitative variables are present as numbers and percent and analyzed by Chi-square test; *significant.

other studies. The incidence of AKI was reported to be 36% in hospitalized patients with COVID-19, in a study from Saudi Arabia conducted by Farooqui *et al*. [23]. In another Saudi Arabian study examining critically ill COVID-19 patients in a multicenter study, AKI occurred in 46.8% of cases [24]. In contrast, AKI is common in critically ill patients with COVID-19 and affects approximately 20-40% of patients admitted to the ICU [25, 26]. About 29% of patients admitted to the intensive care unit have AKI, and the figure is as high as 78% for patients requiring intubation [18]. Several studies have reported that more than 30-50% of hospitalized

Table 3. Comparing different variables among COVID-19 patients with and without acute kidney injury.

Variables	Patients with AKI, n=205 (%)	Patients without AKI, n=135 (%)	p
Age	67.5±11.8	65.4±15.4	0.169
Sex			
Male	128 (62.4)	89 (65.9)	0.565
Female	77 (37.6)	46 (34.1)	
BMI	27.3±6.8	26.4±7.1	0.275
HTN	154 (75.1)	89 (65.9)	0.085
DM2	133 (64.9)	79 (58.5)	0.254
Asthma	19 (9.3)	2 (1.5)	0.003*
IHD	83 (40.5)	45 (33.3)	0.209
CHF	42 (20.5)	24 (17.8)	0.577
CKD	42 (20.5)	26 (19.3)	0.890
HR (beats/min)	98.4±20.2	96.1±17.8	0.286
CRRT	80 (39.0)	0 (0.0)	<0.001*
Need for vasopressors	84 (41.0)	64 (47.4)	0.264
ARDS	164 (80.0)	112 (83.0)	0.571
Temp (℃)	37.9±1.0	37.9±1.1	0.254
RR (breaths/min)	27.9±4.4	27.3±3.9	0.265
GCS	14.55±0.78	14.5±0.78	0.621
Need for MV	48 (23.4)	34 (25.2)	0.796
PaO_2 (mmHg)	62 (51-67)	55 (50-64)	0.784
PaO_2/FIO_2 ratio	64 (56-125)	59 (52-66)	0.087
CRP	68 (34-124)	101 (43-164)	0.006*
Ferritin (ng/mL)	900 (735-1348)	1261 (854-2354)	0.040*
LDH (IU/L)	635 (364- 831)	745 (521-952)	0.014*
D-dimer	2.9 (2.5-3.4)	2.9 (2.55-3.36)	0.137
HB (gm/dl)	11.5±2.2	11.3±2.4	0.359
WBCs (cells/mm^3)	9.6 (8.2-14.8)	12.6 (8.2-16.4)	0.765
Creatinine (mg/dl)	95 (74-133)	88.5 (72-195)	0.004*
BUN (mg/dl)	12 (8.4-18.2)	14 (11-20.4)	<0.001*

Qualitative variables are present as numbers and percent an analyzed by Fisher exact test; quantitative variables present as mean ±SD or as median (IQR) and analyzed by independent samples t-test or Mann-Whitney *U* tests; *significant.

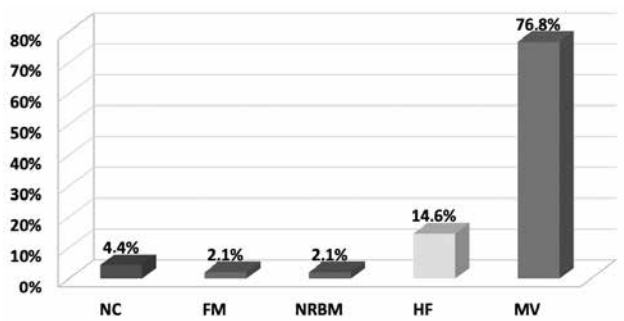

Figure 1. Type of O_2 therapy among the studied patients. NC = nasal cannula; FM = face mask; NRBM = non-rebreather mask function; HF = high-flow; MV = mechanical ventilation.

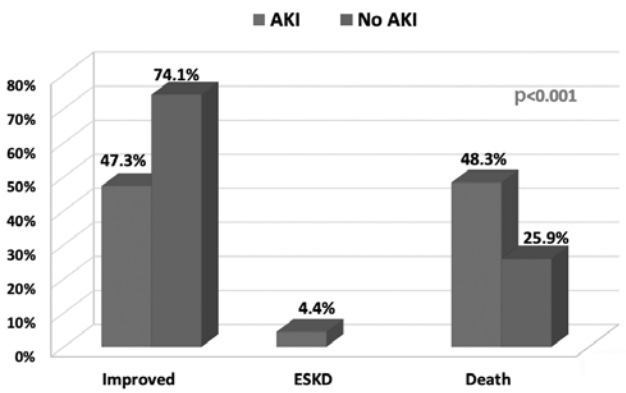

Figure 2. Outcome of COVID-19 pneumonic patients with and without acute kidney injury. ESKD = End Stage Kidney Disease.

patients with COVID-19 develop AKI, with a higher proportion of patients requiring ICU admission [27,28]. Yang *et al*. performed a meta-analysis of 51 studies, and the incidence of AKI in ICU patients was 39% and may reach 42% in deceased patients, and 16.3% of ICU patients required CRRT [29]. Jewell *et al*. analyzed data from hospitalized adults with COVID-19 in two London hospitals and reported that 39% developed AKI (51% in stage 1 and 49% in stages 2 and 3) [30]. Oweis *et al*. conducted a study of AKI in hospitalized patients with COVID-19 from Jordan. The incidence of AKI was 25.3%, and most patients were at stage 1 [31]. CRRT is the preferred treatment for AKI in critically ill patients in the ICU because it provides hemodynamic stability and large fluid removal. Selection of this modality should be based on local experience but is expensive and time-consuming. In this study, 39% of AKI in critically ill COVID-19 pneumonia cases required CRRT, and most of them (81.2%) were in stages 2 and 3. Out of the patients with AKI, 81.2% had ARDS, 43.5% of them required vasopressors, and 76.8% of them required mechanical ventilation. The use of CRRT in our critical patients with COVID-19 was consistent with previous epidemiological studies in which the use of CRRT was required in approximately 44% of patients [16]. Many studies reported that AKI is a common complication in critical COVID-19 cases and occurred in 25-76% of cases, with 5-44% of them requiring CRRT [32,33]. About 35-50.9% of patients with AKI in the ICU associated with COVID-19 pneumonia required CRRT in some studies from the United States [9,15]. Many studies report that 30-40% of COVID-19 infected patients in the ICU require RRT [33,34]. Cummings *et al.* reported that out of 257 critically ill patients with COVID-19, 31% received RRT [27]. In one study it was reported that up to 20% of patients underwent renal replacement therapy (KRT) [5]. This is in contrast to a study from India and Pakistan, which reported that CRRT was required in 22.9% of cases [35]. The incidence of AKI was 43.7%, and 18.2% of patients underwent CRRT, and in this group, 90-day in-hospital mortality was 45.1%. A study by Eriksson *et al*. on CRRT in ICU patients with COVID-19 [36]. In a study from Saudi Arabia, CRRT was required in 18.9% of cases with AKI associated with COVID-19 pneumonia [24]. This is in contrast also to other studies reporting that CRRT was required in 4% to 23% of patients with AKI in critically ill COVID-19 patients [8,37].

In this study, the mortality rate was significantly higher in patients with AKI (48.3%) than in patients without AKI (25.9%), which is often the case in several studies. According to Jewell *et al*., the mortality rate was significantly higher in patients WHO with AKI (44.4%) than in patients WHO without AKI (17.3%) [30]. Alenezi *et al*. performed a scientific review and meta-analysis of the incidence and risk factors of AKI in COVID-19 patients with and without white lung and found that mortality was 38.7% once the studies considered only COVID-19 patients admitted to the department [19]. In a study from Asia conducted by Farooqui *et al*., the presence of AKI was associated with a higher 30-day mortality of 40.7%, compared with 3.7% in patients without AKI [23]. In another study from an Asian country, AKI was found to be much more common in patients who died WHO within thirty days on the ward (74.7%) than in patients who survived WHO on the ward (26.2%) [24]. Eriksson *et al*. performed a study of CRRT in patients with COVID-19 and found that the mortality rate in this group was 45.1% [36]. Our results were lower than those of many other studies. Fominskiy *et al*. found that mortality was higher in patients with AKI (52.9%) than in patients without AKI (38.9%) [37]. Several studies found that overall hospital mortality in patients with COVID-19 and AKI was 66.2% [3,39], and in several studies, it ranged from 60-80% within the AKI-RRT cluster [40, 41]. According to Oweis *et al*., 75% of patients with AKI died within the unit [31]. Compared with patients without AKI, mortality was higher in patients with AKI (32.5% versus 10.4%), and 39.2% of patients with AKI did not recover from urinary organ performance by the end of the follow up period or after ninety days [42]. On the other hand, other studies have not shown AKI to be a risk factor for COVID-19 deaths [30,43].

In this study, the mean age of patients with AKI was 67.5±11.8 years, 62.4% were male, the mean BMI was 27.3±6.8, and the major comorbidities were HTN 75.1%, DM2 64.9%, IHD 40.5%, CHF 20.5%, and CKD 20.5% without significant differences when compared to the group without AKI. These findings were comparable with other studies that showed variable values and percentages. In a study from Saudi Arabia, the mean age was 65 years, 74.5% of patients were male, and the most common comorbidities were DM2 (57.7%), HTN (53.6%), and dyslipidemia (22.7%) [23]. In another study from Saudi Arabia, the mean age was 66 years, 56.7% of participants were male, and the most common comorbidities were DM2 (70.2%), HTN (73.9%), heart failure (21.4%), CHF (16.8%), and a mean BMI of 29.7 [24] also, without significant differences between both groups with and without AKI. In a multicenter ICU study involving 5,866 COVID-19 patients from 55 hospitals in Spain, the main age was 63 years, most of them were men (70.4%), and the most common concomitant diseases were HTN (50.4%), obesity (35.5%), and DM2 (24.9%) [43]. In a systematic review of patients with COVID-19 and AKI, the most common comorbidities were HTN 61.4%, hyperlipidemia 57.1%, DM2 40%, and CKD 22.2 % [44].

In contrast, other studies reported that independent significant predictors of AKI included being older, black American, or male; being overweight; having diabetes; having HTN; having the cardiovascular disease; having a low eGFR or higher interleukin-6 levels; or requiring mechanical ventilation or vasopressor medications [9,10]. Most biomarkers that showed a significant correlation with AKI have been established in relation to the severity of COVID-19, including d-dimer, LDH, neutrophil and leukocyte counts, troponin-I, and CRP [44-47]. In our study, inflammatory markers were high in both groups (AKI and without AKI). Oweis *et al*. reported that comorbidities such as HTN and diabetes, as well as previous renal disease and increasing age, increase the risk of AKI in patients with COVID-19 but not significantly in terms of the degree of inflammation and the increase in CRP [31].

The differences between our results and the others can be explained by many factors: inclusion criteria, quality of the health care system, differences in referral policies, duration of follow up, the experience of the first centers affected by COVID-19 outbreaks, and differences in population characteristics or prevalence of comorbidities.

Study limitations

First: the retrospective nature of the study raises the possibility that differences in the quality of care may affect patient recovery. Second, we used KIGO rather than GMFR to define AKI. Third, some data were not collected, such as urine output, and the mortality rate was used only as in-hospital mortality without post-discharge follow up. In addition, the relation between the percentage of lung parenchyma affected by COVID-19 and the severity of renal involvement was not investigated in the current study. Further prospective studies are recommended to cover these issues.

Conclusion

AKI is common in adults admitted to the intensive care unit with COVID-19 and is associated with an increased risk of death. Early recognition of AKI and appropriate treatment can have a positive impact on the outcome of COVID-19. CRRT is the preferred dialysis method in critically ill ICU patients with AKI.

Abbreviations

AKI: acute kidney injury;
ARDS: acute respiratory distress syndrome;
BMI: body mass index;
BUN: blood urea nitrogen;
CBC: Complete blood count;
CHF: congestive heart failure;
CI: confidence intervals;
CKD: chronic kidney disease;
COVID-19: coronavirus disease 19;
CRP: C reactive protein;
CRRT: continuous replacement therapy;
DM2: type 2 diabetes mellitus;
ECG: electrocardiogram;
FIO2: fractionated inspired oxygen;
GCS: Glasgow coma scale;
GMFR: glomerular filtration rate;
HB: hemoglobin;
HR: heart rate;
HTN: hypertension;
ICU: intensive care unit;
IHD: ischemic heart disease;
IQR: interquartile range,
KDIGO: Kidney Disease Improving Global Outcome;
LDH: lactate dehydrogenase;
MV: mechanical ventilation;
OR: odds ratios;
PaO_2: partial pressure of oxygen tension;
RAAS: renin-angiotensin-aldosterone system;
RR: respirator rate;
RRT: renal replacement therapy;
SARS: severe acute respiratory distress;
WBCs: white blood cells;
WHO: World Health Organization.

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Received for publication: 15 November 2022. Accepted for publication: 13 February 2023.

Multidisciplinary Respiratory Medicine 2023; 18:895
doi:10.4081/mrm.2023.895

Multidisciplinary Respiratory Medicine 2023; volume 18:896

pagepress

REVIEW

Palliative care and end of life management in patients with idiopathic pulmonary fibrosis

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a chronic disease with an unknown etiology that causes deterioration of the structure of the lung parenchyma, resulting in a severe and progressive decline in respiratory function and early mortality. IPF is essentially an incurable disease, with a mean overall survival of 5 years in approximately 20% of patients without treatment. The combination of a poor prognosis, uncertainty about the disease's progression, and the severity of symptoms has a significant impact on the quality of life of patients and their families. New antifibrotic drugs have been shown to slow disease progression, but their impact on health-related quality of life (HRQoL) has to be proven yet. To date, studies have shown that palliative care can improve symptom management, HRQoL, and end-of-life care (EoL) in patients with IPF, reducing critical events, hospitalization, and health costs. As a result, it is essential for proper health planning and patient management to establish palliative care early and in conjunction with other therapies, beginning with the initial diagnosis of the disease.

Key words: End of life; palliative care; health-related quality of life; idiopathic pulmonary fibrosis.

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Conflict of interest: The authors declare no conflict of interest. MDD is a member of the Editorial Board of Multidisciplinary Respiratory Medicine.

Contributions: All the authors made a substantive intellectual contribution, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Ethics approval: Not applicable.

Availability of data and materials: Available from the corresponding author upon reasonable request.

Funding: No funds have been received for this work.

The value of the palliative care in idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is a chronic disease of unknown etiology, characterized by a deterioration of the structure of the lung parenchyma with consequent progressive decline in respiratory function and early mortality, to be comparable in its evolution and in the impact on the quality of life to neoplastic diseases. IPF is characterised by major reductions in quality of life and survival and has similarities to certain malignancies [1]. The health-related quality of life (HRQoL) of the IPF patients is impaired with regard to their general quality of life and the domains of physical health and level of independence. In particular, IPF patients have problems with pain and discomfort, energy and fatigue, sleep and rest, activities of daily living, dependence on medication or treatments, working capacity, ability to acquire new information and skills, participating in and possibilities for recreation/leisure [2]. Despite this, palliative care (PC) in IPF is little used and an organizational difficulty in accessing it is still evident. Due to the unpredictable nature of IPF, early intervention with the initiation of PCs, which include both drug and non-drug therapies, can reduce the burden of symptoms and improve the quality of life of patients and their caregivers [1].

PCs are needed for a wide range of chronic diseases such as cardiovascular disease (38.5%), cancer (34%), chronic respiratory disease (10.3%), AIDS (5.7%), and diabetes (4.6 %) and are based on the patient's needs rather than on the patient's prognosis; this is appropriate at any age and at any stage of severe disease and can be provided in conjunction with curative treatment [3]. According to the World Health Organization (WHO), in fact, PC is defined as "... an approach that improves the quality of life of patients and their families by addressing the problem associated with life-threatening diseases, through the prevention and relief of suffering, through the early identification, flawless assessment and treatment of pain and other physical, psychosocial and spiritual problems" [3]. The erroneous perception that PCs are synonymous with end-of-life (EoL) care deprives patients of their early approach, creating a culture of abandonment without optimizing its effectiveness. PCs can provide better outcomes for patients and their caregivers leading to improved quality of life, often at a lower cost, even if attempts to change traditional health services have had limited success and PCs generally remain only a service that responds to a social need [4].

The ATS/ERS guidelines on IPF management and therapy recommend PCs for the patients, as an adjunct to disease-focused care and should be addressed already during outpatient visits in all patients, in particular those with severe clinical impairment and/or with other comorbidities, both as advance directives of care and as end-of-life issues [5]. It is of note that IPF patients enrolled in PC programs live longer and enjoy a better quality of life, as well as having greater control over symptoms, such as dyspnoea, asthenia, weight loss, psychomotor agitation that accompanies the stages of advanced disease [6].

In a recent study by Younus *et al*. [7], data from 298 patients and their approach to palliative treatment were compared in different clinics; 63% of the patient cohort received PCs. In patients followed in interstitial lung disease (ILD) clinics with multidisciplinary disease management, the primary approach to care resulted in more patients receiving PCs, higher rates of management of non-drug dyspnoea, and treatments with opioids and oxygen therapy, which began 15 and 5 months before death, respectively [7]. Reliance on PC specialist referral for PC initiation outside of the ILD clinic resulted in delayed care [7]. In spite of this, patient referral for palliative care is delayed and most of them die in hospital. Indeed, in a recent retrospective study at the University of Pittsburgh's Simmons Center for ILD, end-of-life decisions were not taken in time and 57% of deaths occurred in hospital, whereas only 13,7% of the deceased had been sent to PCs [8].

Conversations about death and dying can be difficult, and doctors, patients, or family members may find it easier to avoid them altogether and continue treatment, leading to inappropriate end-of-life treatment [4]. In a study by Kalluri *et al*. [9], obstacles to advance care planning (ACP) have been identified, such as unpredictable disease evolution, insufficient and difficult communication, and poor prioritization. Therefore, knowing the end-of-life options can allow patients to make reasoned choices and reduce the risk of deaths in the ICU, as well as guide doctors in implementing early and meaningful conversations, as proposed by the authors in planning the ACP in the IPF (Figure 1) [9]. In this process, practical guidance and training are needed to improve practitioner competence and trust in the ACP, as well as clarity within organizations about role, policy and responsibilities.

The decision-making process in the planning of the PC and the EoL

In recent years, the main goals of PC in IPF have been focused on improving the quality of life by addressing related symptoms, social and psychological needs and seeking to have timely diagnosis and early access to holistic and palliative care treatment. Thus, by applying better supportive care (BSC), defined by all as therapeutic interventions aimed at controlling symptoms in patients with progressive diseases, PCs offer patients the opportunity to improve their quality of life, reduce the burden symptoms with a reduction in unplanned hospital admissions [10].

A potential model of PC for IPF patients was described by the study of Veigh *et al*. [11], which proposes three levels of PC for patients with ILD, COPD and bronchiectasis, supporting the ongoing holistic assessment of patient needs (Figure 2). The first level supports a holistic approach to care, that is introduced with the diagnosis of the disease and should include both general and specialized pulmonary PCs. The beginning of the complexity of symptoms leads to the second level, suggesting that health professionals must also evaluate the need to introduce specialized PC services. When patients develop complex symptoms that general practitioners and pulmonologists feel they are no longer able to manage effectively, they move to level three of the model, which proposes to go directly to specialized PC services. This study reinforced the importance of proactive PC that identifies the needs of the individual patient, and it is not influenced by their prognosis [11].

Starting from the three levels of complexity, it is possible to identify levels of intensity and appropriate settings for the provision of PCs, which are classified into three macro-areas: palliative approach, shared care and specialist PCs. All three levels of delivery can be integrated within the Local Palliative Care Network. For the palliative approach, the most appropriate setting is represented, in relation to the various phases of the disease and its severity, respectively by the patient's home, by the hospital (outpatient or in hospital), by extra-hospital facilities, by residences nursing homes and health residences for the disabled.

For patients of the second or intermediate level of complexity of needs, the team of specialist PCs acts by sharing the treatments and therapeutic objectives with the patient and agreeing them with a plurality of health professionals who participate in the care, each with their own specific skills and most appropriate areas of inter-

vention at home, or in the hospital to support the ward team, in the hospital or specialist outpatient clinic of PCs.

For a high level of complexity of the needs of the patient and of the caregiver/family unit, the responsibility for care lies with the PC specialist team. The GP and the branch specialist can continue to play a role mainly aimed at fostering the continuity of the treatment path and supporting the relational aspects. The most consistent care setting is the hospital or even the home through being taken care of by teams of specialized, multidisciplinary and dedicated PCs (home UPC) [12-14].

End of life decision making in medical practice is not a straightforward process; in fact, it involves not only legal but also ethical obligations. In this regard, it is worth to underline the cultural path that has developed in Italy since 2003 and culminated in 2017 with the approval of a specific law, which is based on the principles of protection of life, health, dignity, and self-determination of sick person [15]. This law, in fact, protects the right to life, health, dignity and self-determination of the person and establishes that no health treatments can be started or continued without the free and informed consent of the person concerned, except in the cases expressly provided for from law. Everyone has the right to know their health conditions and to be fully informed and updated to them about the diagnosis, prognosis, benefits and risks of the indicated diagnostic tests and health treatments, as well as about possible alternatives and the consequences of any refusal of medical treatment and diagnostic assessment or the renunciation of the same. All this has to be recorded in the patient's medical record and electronic health record [15]. The law also explicitly refers to consent an Advance Planning/Shared Care (APC) as a tool capable of enhancing the Advance Treatment Planning (ATP) witnessed by the role of the Trustee [15].

However, religious and cultural values, often superimposed on social or psychological needs, must be recognized and considered [16]. Notably, the study of Evangelista et al. that examined thirty-nine publications on the relevance of the spiritual dimension in the care of patients with palliative care, pointed out that religious and spiritual beliefs and performing spiritual practices, like meditation and praying, for example, can reduce anxiety and distress caused by terminal diseases, because these facilitate easing patients' mind [17]. It is also important to discuss both the possibility of "not-resuscitating" (DNR or AND - allow natural death) and "not-intubating" (DNI), with patients and their families, to avoid unnecessary therapies or unwanted interventions, upon entering the hospital in the terminal phase [18]. Rajala and colleagues have shown that the orders not to resuscitate (DNR) and the decisions of EoL come late and that the therapies probably continue until the last days of life, not considering the futility of these interventions. It sometimes may hard to make the decision not to ventilate a patient referred for acute respiratory failure. Decision not to ventilate usually depends on assessment of futility of care depending on poor short-term prognosis, patient's wishes and the high probability of poor quality of life in the future. Before making such decision doctors usually try to look for evidence on previous outcomes in similar cases [18]. It is underlined that medical interventions, such as CPR and ICU care, which are often considered futile by current medical standards, are not futile at all, but have significant ritual-

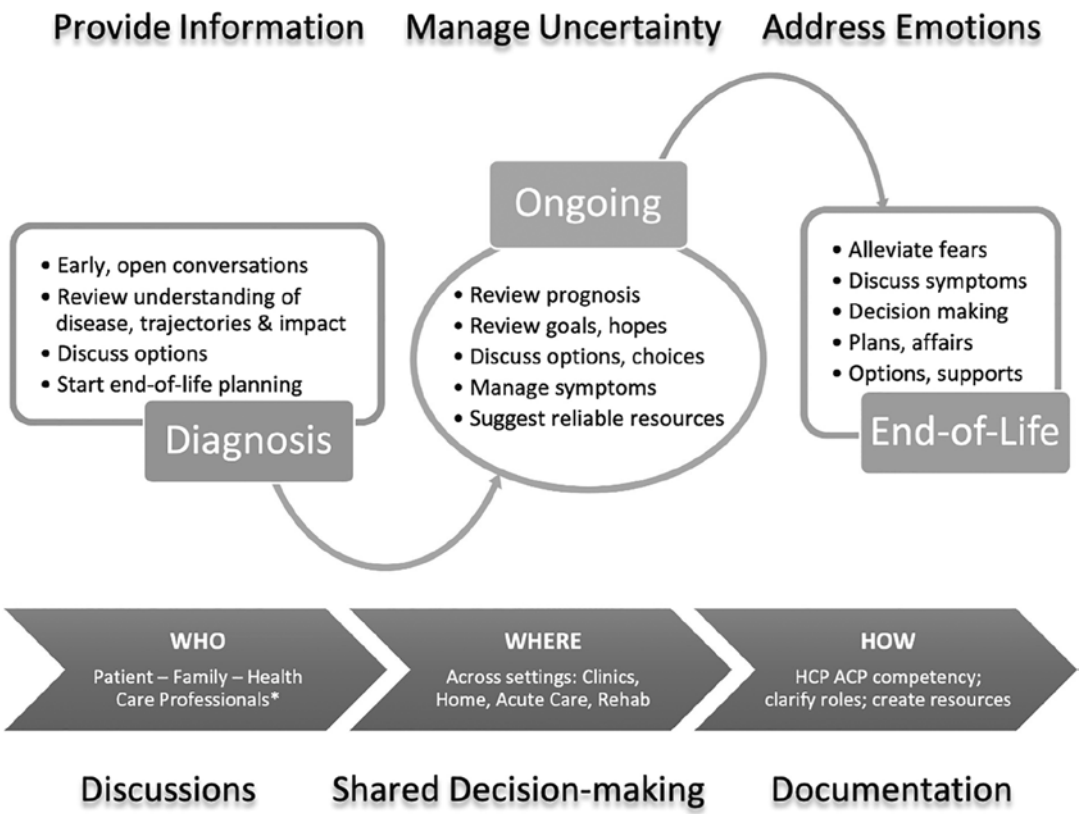

Figure 1. Framework of the Advance Care Planning (ACP) decision program under IPF. HCP, healthcare professionals involved; ACP, advance care planning. *Specialists and general practitioners, nurses, health professionals. Retrieved from: Kalluri M, *et al.* Am J Hosp Palliat Care 2022;39:641-51; with permission. License: https://creativecommons.org/licenses/by-nc/4.0/

istic value and serve important social functions in the process of dying. This work offers a new perspective on the ethical debate concerning medical futility and provides a means to explore how the social value of treatments may be as important in evaluating futility as biomedical criteria [19,20]. Most patients with IPF die in hospital with life-prolonging procedures and frequent use of opioids, this is an indicator of intent to relieve symptoms, but decisions of EoL still occurs very late. Advance care plans are the first discussion for EoL management and could improve PC for patients with IPF [18,21].

The Italian Society of Anesthesia Analgesia Resuscitation and Intensive Care (SIAARTI), in the last update [22], addressed the treatment of intensive care in terminal patients, since still today many clinicians implement them as a therapeutic option, especially when a defensive logic is prevailing. However, in recent years there has been a more attentive approach to the real needs of the sick person, in relation to the opportunity to undertake or continue an intensive care plan. Therefore, a "proportionate" treatment, that is legitimate and ethically licit has been identified only if, in addition to being clinically appropriate, it is consciously accepted by the sick person and is able to consistently be included in the person's life plan [22]. Anyway, all of this has not found adequate application during the recent COVID-19 pandemic, which has further fuelled the fear of death and reinforced the idea of health services as the sole guardians of death. The doctors and, above all, the relatives of the deceased person were absolutely not prepared for the idea of death, always present and/or possible, and the patients died of medical death, often alone in hospitals and intensive care

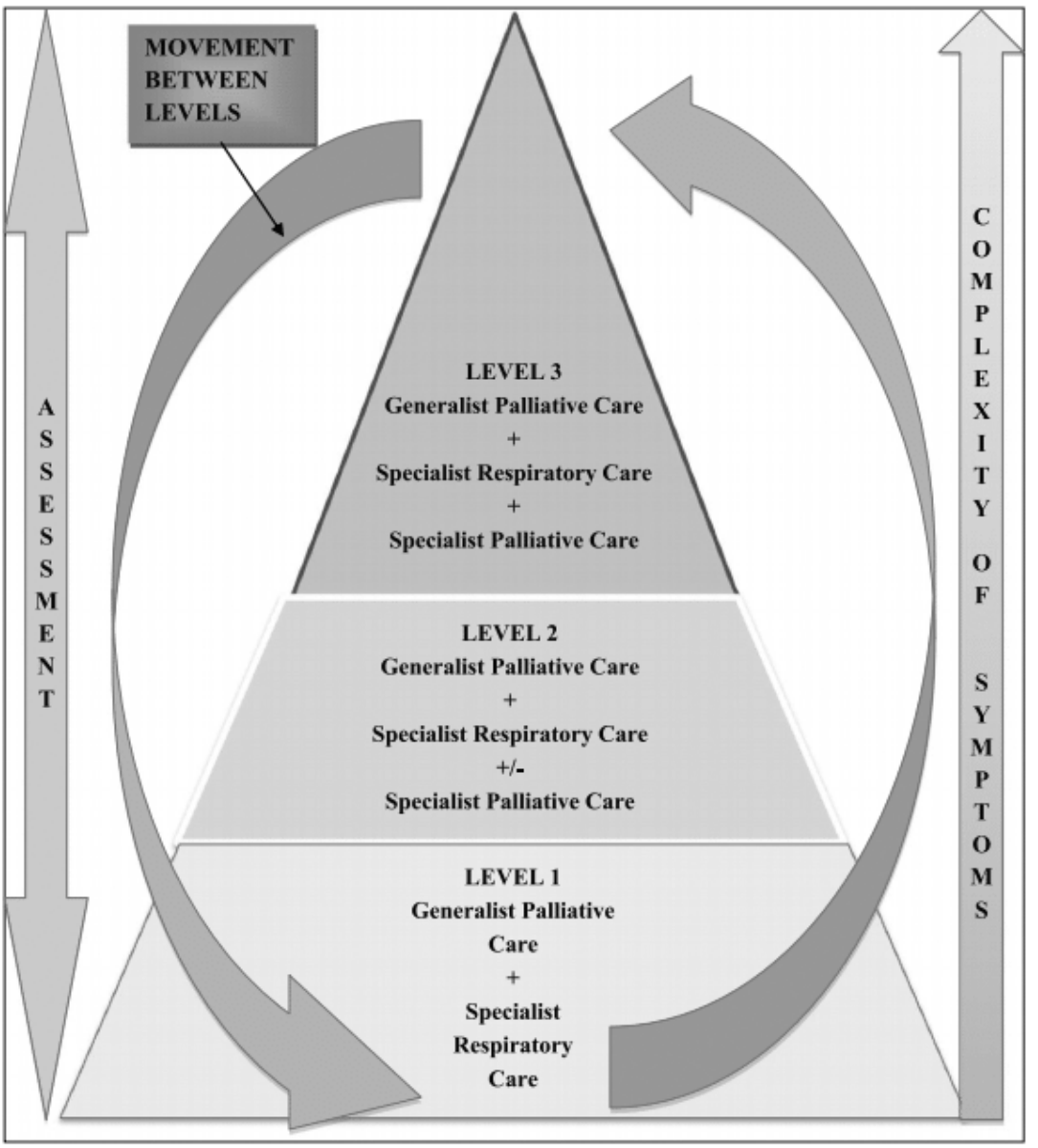

Figure 2. Palliative care model for patients with non-malignant respiratory disease. Modified from: Veigh CM, *et al.* BMC Palliat Care 2018;17:6; with permission. License: http://creativecommons.org/licenses/by/4.0/

units, unable to communicate with the family if not remotely [4]. It is important underline the COVID -19 pandemic forced health staff and decision makers to cope with a desperate shortage of resources (obliging to ration resources almost in a logic of combat medicine), setting up a scenario which could sooner or later materialize in public health services and, in such a context, should be important the role of telemedicine [23].

As the pandemic is hopefully coming to an end, there is no concrete evidence of a change in welfare, but only contrary signs that show how governments prioritize attempts to reduce only the number of deaths and not the extent of suffering, placing great emphasis on providing intensive and sub-intensive care and more lung ventilators, but not laws and programs on PCs. Mourning has been neglected, on the other hand anxiety about death and dying seem to have increased [4].

This pandemic period should help political leaders and health authorities to move as quickly as they can to ensure that there are enough resources, including personnel, hospital beds, and intensive care facilities, for what is going to happen in the next years [24]. Moreover, it would be necessary to solve organizational problems to prepare the health system to respond to a similar emergency in a joint, coherent, and homogeneous way across the country, as planned in the WHO document. In this perspective, Pulmonary Units and specialists can play a fundamental role in coping with the disease not only in hospitals, as intermediate care units, but also at a territorial level in an integrated network with GPs [25]. All of this may have had negative implications even in areas not strictly related to the pandemic, such as in the case of patients with IPF.

The timing of palliative care and EoL treatments

Care for people at the EoL, rather than being guided by rigorous protocols, should be based on clinical evidence and tailored to the patient's preferences and needs, in order to create individualized care plans in an early timing [16]. The guidelines of the General Medical Council on the EoL provide recommendations on communication and shared decision-making and constitute a useful resource for all health professionals [26]. In this regard, it is essential to recognize the EoL condition of patients with IPF by evaluating changes in signs/symptoms, such as to be able to identify them within the multidisciplinary team. Treating and taking care of patients is defined by a "simultaneous care" program that must start from the early stages of the disease (Figure 3) [27] as the progression of the disease will lead to an intensification of palliation inversely proportional to the reduction in the efficacy of pharmacological treatments, traditional supportive, and rehabilitation [27-29]. In a study by van Manen *et al*., a new model is proposed for the continuous treatment of IPF structured for comprehensive care, including palliative and EoL care. With this model, summarized in an "ABCDE" scheme (Figure 4), patient support was achieved by providing relevant information and adequate support and by providing care that improves patient comfort, focusing on the treatment of symptoms and comorbidities [30].

In recent years, the main goals of PC in IPF have been focused on improving the quality of life by addressing related symptoms, social and psychological needs, and seeking to have timely diagnosis and early access to holistic care and palliative treatment. Patients with IPF present many symptoms during the natural history of the disease and there is a need to use better supportive care (BSC), defined as the set of interventions and the multi-professional approach, aimed at improving and optimizing HRQoL (Table 1) [31]. Almost all patients with IPF experience progressive dyspnoea, with a greater or lesser impact on their quality of life. Dyspnoea and the resulting anxiety, in addition to decreased exercise tolerance, lead to functional disability and social limitations. In the management of dyspnoea, it is important to exclude comorbidities such as: pulmonary hypertension, heart disease, muscle weakness, sleep disturbances, and psychosocial factors [32]. Frequent use of opioids is used in PC phases, reflecting a great need to control dyspnoea in end-stage patients. Despite this, no

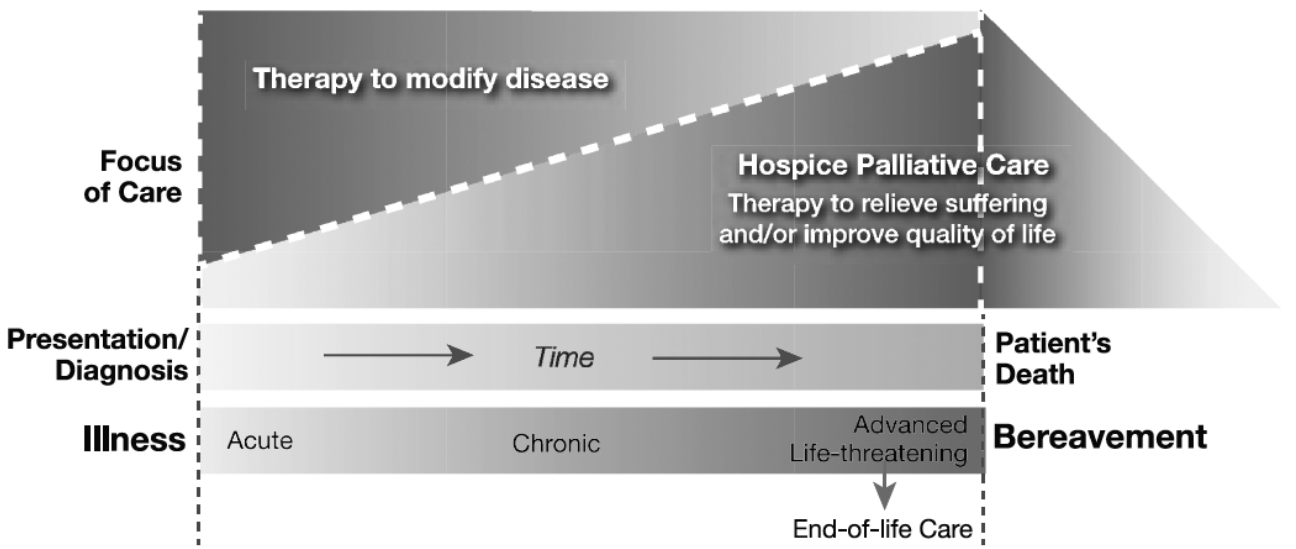

Figure 3. The role of hospice palliative care during illness. Retrieved from: A Model to Guide Hospice Palliative Care, Canadian Hospice Palliative Care Association, 2013; with permission.

controlled studies support the use of opioids in dyspnoea in patients with IPF, as they are often seen as EoL care, although it is widely used in refractory dyspnoea in general [32,33]. In this regard, in a study of 27 patients with IPF treated with opioids for worsening dyspnoea, none showed any significant increase in $PaCO_2$ or reduction in PaO_2 and all patients experienced significant relief of dyspnoea and decreased respiratory rate. The authors concluded that opioids reduce work of breathing, hence decrease respiratory rate, but do not affect alveolar ventilation [34]. This is also supported by the results of other small retrospective studies and, therefore, opioids should be evaluated as an early palliative treatment in these patients [35,36]. The poor prognosis of the disease and its progressive course can underlie feelings of sadness, fear, anxiety and panic. In a Swedish study, anxiety was more common (66%) in patients with IPF than in cancer patients (17%), so out of them 25% received antidepressants and 44% received anxiolytics [37]. Depressive symptoms are important predictors of quality of life and their treatment has not been studied in IPF but can certainly be alleviated with a supportive psychological care strategy [38]. Another reported symptom of IPF is cough which has been associated with disease progression. The exact mechanism underlying cough in patients with IPF is unknown but is most likely "multifactorial" and due to mechanical, biochemical and sensorineural changes, as well as to the associated comorbidities. Low-dose steroids are routinely prescribed for cough in IPF, although there is little data to support their effect [39]. Recent evidence suggests that the antifibrotic drug pirfenidone may have a positive effect on cough, not as effective as the more recent nintedanib, whose effect on cough is still unknown. Although there are no convincing data on cough suppressants in IPF, some patients report relief from these agents [40]. Another non-negligible symptom in patients with IPF is reduced exercise tolerance, which with the progression of the disease leads to less physical activity of the patients, negatively influencing social participation. Pulmonary rehabilitation (PR) can be an excellent therapeutic approach, offering significant short- and long-term improvements in exercise capacity, HRQoL and degree of dyspnoea. Therefore, rehabilitation should be recommended as a standard treatment for patients with IPF with early referral, allowing patients to benefit most from it predominantly when they are still in good physical condition [41]. In the general framework of palliative treatment, another important point is the management of respiratory failure which represents a natural evolution of IPF. In its approach, mechanical ventilation is rarely effective and must be used judiciously in these patients [42]. Non-invasive mechanical ventilation (NIV) has been used to relieve dyspnoea as a palliative treatment and in acute chronic obstructive pulmonary disease [43]. The benefit of using NIV in symptomatic therapy of patients with IPF has not been demonstrated and, therefore, NIV is not routinely recommended. A study on a large cohort of patients with IPF has shown that mechanical ventilation is associated with a mortality rate of 50%, but that its palliative use may be appropriate in relieving dyspnoea in selected patients. However, mechanical ventilation can be a useful bridge for lung transplantation, provided that the transplant can be performed quickly [44]. Contrary to NIV, oxygen therapy is recommended for IPF patients with hypoxemia, so it is not surprising that most patients with IPF have received oxygen therapy. An effective alternative to NIV and/or oxygen therapy alone is high flow nasal cannula therapy (HFNC), which provides a high flow of heated and humidified oxygen. Oxygen therapy with HFNC is a relatively new method for the treatment of hypoxemic respiratory failure and dyspnoea. In a randomized controlled trial of normocapnic patients with severe hypoxemic respiratory failure, HFNC was comparable to NIV in reducing the need for invasive ventilation, but was superior in relief of dyspnoea and reduction in respiratory rate [45]. HFNC is a ventilation technique that requires less training from hospital medical and nursing staff than NIV, so it can be applied to a greater number of patients even in ordinary wards outside the intensive setting [46]. HFNC can be used for severe respiratory failure hypoxia of any cause, including interstitial lung disease, cancer, and pneumonia, but data are still scarce on its use in patients approaching end of life.

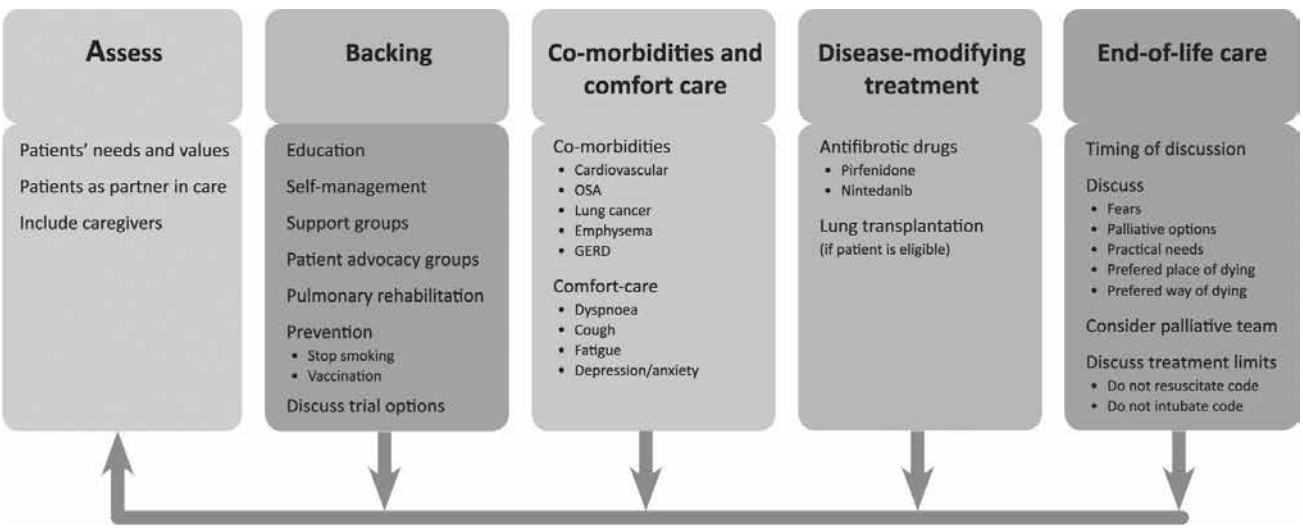

Figure 4. The ABCDE model shows a possible structured approach for the comprehensive care of IPF, including palliative care throughout the course of the disease. Retrieved from: van Manen MJ, et al. Ther Adv Respir Dis 2017;11:157-69; with permission.

In the absence of treatments, which can slow and/or modify the evolution of fibrosis, with significant effects on respiratory failure, future research should aim at patient-centered results as well as HRQoL, both as experimental endpoints and as important measures of efficacy of therapeutic interventions [47]. In chronic diseases, including IPF, it becomes essential to establish Diagnostic-Therapeutic Assistance Path (DTAP) based on guidelines already prepared and shared. In this regard, a DTAP for IPF has recently been drawn up in the Campania Region (Italy), where PC and EoL therapy delivered by a multidisciplinary team of doctors, nurses and social workers in any care setting (home or hospital), represent a real strength [48].

Conclusions

Palliative care provides excellent outcomes for patients and their caregivers and leads to improved quality of life, often at a lower cost, but attempts to raise awareness in the NHS have had limited success and PCs generally remain only a few real social needs with a poor response from basic, hospital and/or territorial care services. It should be desirable for healthcare professionals to recognize that advance care planning is not about bringing the patient closer to the end of life, but a holistic communication process that addresses symptoms, psychosocial and emotional needs, alleviates fears, promotes hope and arouses involvement.

In this process, the following items are necessary: guidelines, greater training and skills of health professionals, greater confidence in advance planning of care, greater clarity within health and social organizations regarding the role, policy and responsibilities around to palliative care. Death, dying and bereavement have become increasingly unbalanced and relationships and interpersonal relationships are being replaced by health professionals and operational protocols. EoL care has become highly medicalized and families and communities have been pushed to the side-lines, losing familiarity and confidence in supporting death, dying and bereavement. Furthermore, the Lancet Commission on Global Access to PC and Pain Relief has shown that the relationship with death in low- and middle-income countries is unequal, as the rich ones receive excessive care while the poor ones, the majority, receive little or no attention or relief from suffering and have no access to opioids [49].

IPF is characterized by significant reductions in the quality of life and survival and, in its evolution, can be compared to a neoplastic pathology. However, PC is still conspicuously inaccessible to many patients with IPF compared to oncological diseases [1]. In the terminal stages of the disease, patients with IPF suffer from debilitating cough with severe dyspnoea, as well as significant physical and functional impairment, associated with significant comorbidities such as pulmonary hypertension, cardiovascular disease and lung cancer, which worsen their quality of life and survival.

Finally, integrating palliative care more and more into the clinical approach in patients with IPF means trying to evaluate multidisciplinary care pathways, encouraging treatments with oxygen, opiates, alternative therapies like HFNC, and rehabilitation for symptom control, already from the initial stages of the disease. Therefore, although the impact of PCs on HRQol in IPF has not been fully demonstrated yet, there is no doubt that early supplementation of palliative care can undoubtedly improve symptom management, HRQol and EoL care, reducing critical events and hospitalization, as well as healthcare costs.

Table 1. Better supportive care (BSC) for managing the most frequent signs and symptoms in patients with idiopathic pulmonary fibrosis (IPF). Reproduced from: Ferrara G, *et al.* Eur Respir Rev 2018;27:170076; with permission. License: https://creativecommons.org/licenses/by-nc/4.0/

Symptom/factors limiting QoL	Tool for assessment	Interventions
General well-being	EQ-5D	Management of symptoms influencing QoL
	SF-36/RAND	Mindfulness/meditation
	SGRQ-IPF#	Physical rehabilitation¶
	K-BILD#	Nutritional support
	ATAQ-IPF#	
Dyspnoea	mMRC	Physical rehabilitation¶
	SGRQ-IPF#	Supplemental oxygen
	K-BILD#	Treatment of PH with sildenafil¶
	ATAQ-IPF-cA#	Pharmacological interventions (morphine/benzodiazepines)¶
	UCSD SOB#	
Cough	LCQ#	Poor effect of usual anti-tussive drugs
	VAS#	Systemic steroids
	CQLQ#	Thalidomide¶
		Gabapentin
		Opiates
		PSALTI
Anxiety/depression	EQ-5D	Counselling/cognitive behavioural therapy
	SF-36/RAND	Antidepressants
	K-BILD#	Physical rehabilitation
	SGRQ-IPF#	Nutritional support (loss of appetite)
	ATAQ-IPF-cA#	
Weight loss	NA	Nutritional support
Comorbidities	NA	Treatment of PH with sildenafil¶
		Anti-reflux measures in patients with GORD

Abbreviations

AND, allow natural death;
APC, advance planning/shared care;
ATP, advance treatment planning;
BSC, better supportive care;
DNI, not-intubating;
DNR, not-resuscitating;
DTAP, Diagnostic-therapeutic assistance pathways;
EoL, end-of-life care;
HFNC, high flow nasal cannula therapy;
HRQoL, health-related quality of life;
ILD, interstitial lung disease;
IPF, idiopathic pulmonary fibrosis;
NIV, non-invasive mechanical ventilation;
PC, palliative care;
WHO, World Health Organization.

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Received for publication: 15 November 2022. Accepted for publication: 25 January 2023.

Multidisciplinary Respiratory Medicine 2023; 18:896
doi:10.4081/mrm.2023.896

SHORT REPORT

Management of interstitial lung disease in patients with autoimmune disease-related interstitial lung disease

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ABSTRACT

Interstitial lung disease (ILD) is a common manifestation of systemic autoimmune diseases. A proportion of patients with autoimmune disease associated-ILDs develop progressive pulmonary fibrosis. Regular monitoring of patients with pulmonary fibrosis is recommended to enable prompt detection of progression and initiation or escalation of therapy if needed. However, there is no established algorithm for the treatment of autoimmune disease associated-ILDs. In this article, we present three case studies that demonstrate the challenges in the diagnosis and management of patients with autoimmune disease associated-ILDs and the importance of taking a multidisciplinary approach to their care.

Key words: rheumatoid arthritis; dermatomyositis; polymyositis; pulmonary fibrosis; systemic scleroderma.

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Contributions: the authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). All authors have made substantial contributions to the acquisition of data, analysis and interpretation of data and revising the article critically for important intellectual content. All authors read and approved the final manuscript.

Conflict of interest: TK reports personal fees from Boehringer Ingelheim Pharmaceuticals, Inc. United Therapeutics, Inc. and PureTech Lyt-100. JRW reports personal fees from Boehringer Ingelheim Pharmaceuticals, Inc. KGD and ASA have no competing interests to disclose.

Ethics approval and consent to participate: no ethical committee approval was required because this article does not report a study with human participants or animals.

Availability of data and material: additional anonymized data on these case studies may be available on request. Please contact the corresponding author.

Funding: the article processing charge for this article was paid by Boehringer Ingelheim Pharmaceuticals, Inc.
The authors did not receive payment for the development of this article.

Introduction

Interstitial lung disease (ILD) is a common manifestation of systemic autoimmune diseases including rheumatoid arthritis (RA) [1], systemic sclerosis (SSc) [2] and polymyositis/dermatomyositis [3]. The course of ILD is variable. Some patients with fibrosing autoimmune diseases associated-ILD develop a progressive fibrosing phenotype characterized by increasing fibrosis on high-resolution computed tomography (HRCT), decline in lung function, and early mortality [2-4]. Immunosuppression is the standard of care to treat autoimmune diseases and has been shown to slow the progression of SSc-ILD [5-7]. Recently the interleukin-6 (IL-6) receptor antagonist tocilizumab was approved by the FDA for slowing the rate of decline in lung function in patients with SSc-ILD. There are limited data on the efficacy of immunosuppressants in patients with autoimmune disease-related ILDs other than SSc-ILD [8-17]. Recently, rituximab was shown to be effective in improving lung function in patients with autoimmune disease-related ILD including SSc, idiopathic inflammatory myositis (including polymyositis or dermatomyositis), or mixed connective tissue disease (CTD) with associated severe or progressive ILD, with fewer adverse events compared to cyclophosphamide [17]. Based on data from randomized placebo-controlled trials showing that it slows decline in lung function in patients with SSc-ILD [18], idiopathic pulmonary fibrosis (IPF) [19] and progressive fibrosing ILDs other than IPF [20], nintedanib has been approved by the FDA and other regulators for the treatment of these ILDs. Data on the benefits of combination therapy for autoimmune disease-related-ILD remain sparse, and there is no established algorithm for the initiation or escalation of pharmacotherapy in these patients. In this article, we discuss three case studies that illustrate the challenges in the diagnosis, monitoring and management of autoimmune disease associated-ILDs.

A case of progressive RA-ILD

A 62-year-old male with coronary artery disease treated with stent placement ten years prior was evaluated in the pulmonary

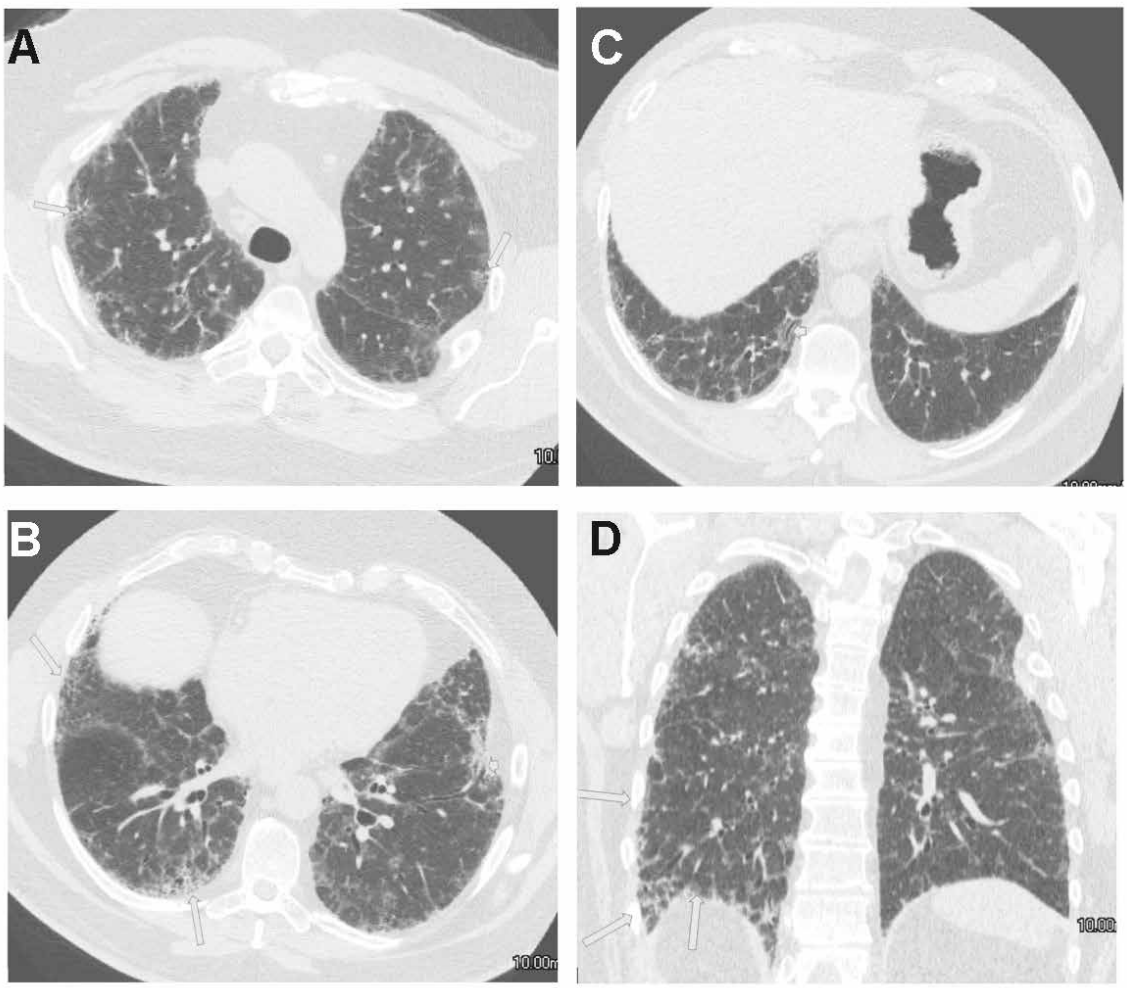

Figure 1. HRCT scans at presentation from a patient with RA-ILD. Axial image at the level of the aortic arch (A), axial image at right inferior pulmonary vein ostium (B), axial image just above the hemidiaphragms (C), and coronal HRCT image (D) illustrating the craniocaudal disease distribution. Areas of peripheral reticulation (arrows in A and B) are more severe in the bases. Note areas of traction bronchiectasis/bronchiolectasis (arrowheads in C). No definitive honeycombing is seen and the apparent ground glass densities are limited to areas of reticulation, likely reflecting microscopic fibrosis. The right basilar reticulation extending up the lateral sidewall (arrows in D) is common in a UIP pattern of lung injury. This is a probable UIP pattern given the lack of features inconsistent with UIP.

clinic after presenting to his primary care physician with dyspnea on exertion. He was unable to walk more than 500 meters without feeling out of breath. He also complained of a dry cough throughout the day without aggravating or relieving factors. A review of symptoms revealed joint pain, especially in the hands, associated with morning stiffness, and gastroesophageal reflux disease (GERD). He was a former smoker (30 pack/years) who had quit smoking a few months prior to his clinic visit. He had worked as a machinist for 32 years and been exposed to fine metal particles but had no other environmental exposures. His medications included aspirin, atorvastatin and ezetimibe. His physical examination was significant for bilateral basal crackles on respiratory exam and swelling in his bilateral metacarpophalangeal (MCP) joints.

Serological studies were notable for an increased rheumatoid factor level (354 IU/mL) and IgG anti-cyclic citrullinated peptide (anti-CCP) antibody level of >150 units. Pulmonary function tests (PFTs) showed a forced vital capacity (FVC) of 2.5 L (50% predicted), forced expiratory volume in one second (FEV_1) of 2.10 L (60% predicted), FEV_1/FVC ratio of 70% (84% predicted), total lung capacity (TLC) of 3.56 L (48% predicted), residual volume (RV) of 1.06 L (41% predicted), and diffusion capacity of the lung for carbon monoxide (DLco) of 14 mL/mmHg/min (48% predicted). Supplemental oxygen was required on six-minute walk testing with a nadir oxygen saturation of 91%. Cardiac echocardiography showed a left ventricular ejection fraction (LVEF) of >55%, normal right ventricular systolic function and borderline mitral valve prolapse. Chest roentgenography (X-ray) demonstrated diffuse reticulations. HRCT demonstrated a probable usual interstitial pneumonia (UIP) pattern (Figures 1 and 2). A barium esophagram was negative for laryngeal penetration or tracheal aspiration.

The patient was referred to a rheumatologist who confirmed a diagnosis of RA. After multidisciplinary discussion (MDD) including review of the clinical features, imaging and serologies, a diagnosis was made of RA-associated ILD (RA-ILD). Treatment options were discussed with the patient, and he was started on mycophenolate mofetil, in addition to pantoprazole for GERD. The patient developed fatigue and nausea soon after starting mycophenolate mofetil and so, after confirming thiopurine methyl transferase activity levels were normal, he was switched to azathioprine. He was unable to tolerate azathioprine due to nausea. Meanwhile, the patient developed increased joint pain in his bilateral MCP joints. His chest imaging was predominantly fibrotic and did not reveal ground glass opacities. After MDD between pulmonologists and rheumatologists, a decision was made to treat his joint pain with hydroxychloroquine 400 mg daily and oral methotrexate 15 mg weekly with daily folic acid. Close follow up on a quarterly basis was planned, including PFTs. The patient underwent annual six-minute walk testing and echocardiography to screen for pulmonary hypertension. Over the next two years, his joint symptoms were well controlled, with stable PFTs and no changes in echocardiogram.

Two years after his first visit, the patient had worsening dyspnea on exertion. His spirometry revealed an FVC of 1.74 L (41% predicted), FEV_1 of 1.74 L (45% predicted) and DLco of 9 mL/mmHg/min (32% predicted). On six-minute walk testing, he required 4 L of oxygen. HRCT at this time demonstrated progressive fibrosis with a typical UIP pattern with clear honeycombing (Figure 3). His echocardiogram was similar to baseline. He was admitted to hospital and underwent a left heart catheterization, which revealed mild non-obstructive coronary artery disease. Right heart catheterization was not consistent with pulmonary hypertension. Given the progression of ILD and persistent extrapulmonary symptoms, the decision was made in an MDD to discontinue methotrexate and initiate rituximab. Three months after his first rituximab infusion, he was admitted to the hospital with fever. Laboratory tests were significant for a white count of 1970 cells per mL of blood with an absolute neutrophil count of 0. Work-up revealed chest wall cellulitis, for which he was treated with broad spectrum antibiotics. After consultation with the hematology team, it was deemed that his neutropenia was secondary to rituximab therapy. He was discharged from hospital after his white count had recovered to 3740 cells per mL with a ten-day course of amoxicillin-clavulanate. During follow up in the pulmonary clinic two weeks after discharge, spirometry was notable for an FVC of 1.88 L (36% predicted), FEV_1 of 1.58 L (41% predicted) and DLco of 11.8 mL/mmHg/min (41% predicted). Due to worsening FVC and respiratory symptoms, nintedanib was initiated for progressive fibrosing ILD and the patient was evaluated by the lung transplant team.

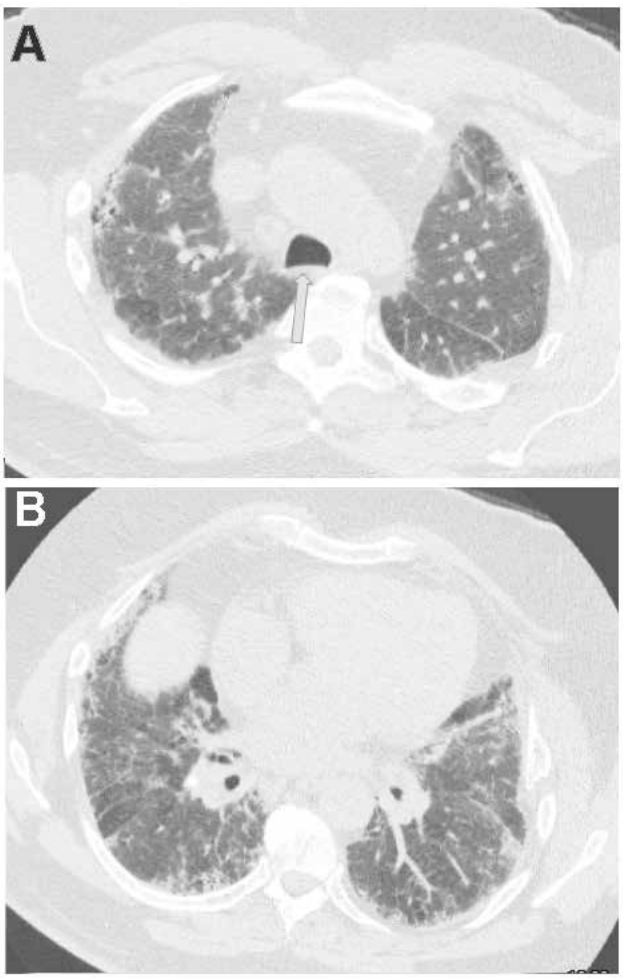

Figure 2. Expiratory HRCT images at presentation from a patient with RA-ILD at the level of the aortic arch (A) and left inferior pulmonary vein ostium (B). Images demonstrate a normal homogenous increase in lung attenuation with expiration and no significant air trapping. Significant air trapping (diffuse in three or more lobes) would suggest an alternative diagnosis such as fibrotic hypersensitivity pneumonitis. Note the flattening of the membranous trachea (arrow) suggesting adequate expiratory effort. If the trachea maintains a rounded configuration on both the inspiratory and expiratory scans, this suggests the expiratory effort was poor, which limits the ability to assess for air trapping.

Three months later, his oxygen requirement had increased to 5 L on exertion with no change in his echocardiogram. HRCT at this time demonstrated no appreciable change, with no imaging manifestations of a superimposed infection or an acute exacerbation. After discussion with the rheumatology team, a plan was made to initiate intravenous cyclophosphamide, but in the interim, the patient was listed for a lung transplant. He received a single lung transplant and was doing well 9 months later.

A case of SSc-ILD

A 50-year-old woman presented at our tertiary referral center for evaluation of ILD. She had no medical history other than back and knee surgeries until a few months prior, when she noticed skin tightening on her hands and subsequent joint pain. She had no family history of pulmonary disease or autoimmune conditions. She had never smoked and had no occupational or environmental exposures. She was positive for Scl-70 and had occasional Raynaud's phenomenon, GERD, sicca, and telangiectasias. She was diagnosed with SSc by her rheumatologist. After a chest X-ray, she was told that there might be some scarring in her lungs. She was started on oral prednisone 20 mg daily and transitioned to mycophenolate 1 g twice daily. She was started on esomeprazole 40 mg daily to treat symptoms of acid reflux. By the next month, she noted worsening dyspnea, which progressed to limiting her daily activities, as well as a non-productive cough which prompted referral to our ILD center. No fevers, chills, chest pain, or pedal edema were noted.

On initial exam at our center, she had an oxygen saturation of 97% at rest. She had bilateral lower lung field dry crackles on exam, and sclerodactyly in both hands. No fingertip ulcerations were noted. Her initial pulmonary function tests revealed FVC of 2.28 L (56% predicted), FEV_1 of 1.98 L (62% predicted), FEV_1/FVC ratio of 87%, TLC of 3.49 L (62% predicted) and DLco of 6.6 mL/mmHg/min (27% predicted). She did not require oxygen during a six-minute walk test. Her serologies were confirmed positive for Scl-70 and anti-nuclear antibody. HRCT demonstrated a non-specific interstitial pneumonia (NSIP) pattern of lung injury (Figures 4 and 5). With this clinical presentation, a diagnosis of SSc-ILD was confirmed by MDD. Mycophenolate was titrated to 1.5 g twice daily. Her laboratory measurements, including white blood cell count, were monitored quarterly.

An echocardiogram showed LVEF >55%, right ventricular systolic pressure 30-40 mmHg and normal right ventricular systolic function. She underwent right heart catheterization, which showed mean pulmonary artery pressure of 25 mmHg (38,13 mmHg) with normal pulmonary capillary wedge pressure. She experienced progressive worsening of dyspnea and cough. Her skin symptoms remained stable. PFTs 6 months later showed an FVC of 2.20 L (54% predicted), FEV_1 of 1.96 L (61% predicted), FEV_1/FVC ratio of 89%, and DLco of 9.5 mL/mmHg/min (39% predicted). Her HRCT showed an increase in fibrotic changes (Figure 6). She was started on nintedanib 150 mg twice daily, in addition to the mycophenolate mofetil. Six months later, she continued to have exercise limitations but her PFTs had stabilized. PFTs showed an FVC of 2.16 L (53% predicted), FEV_1 of 1.96 L (62% predicted), FEV_1/FVC ratio of 89%, and DLco of 8.5 mL/mmHg/min (35% predicted).

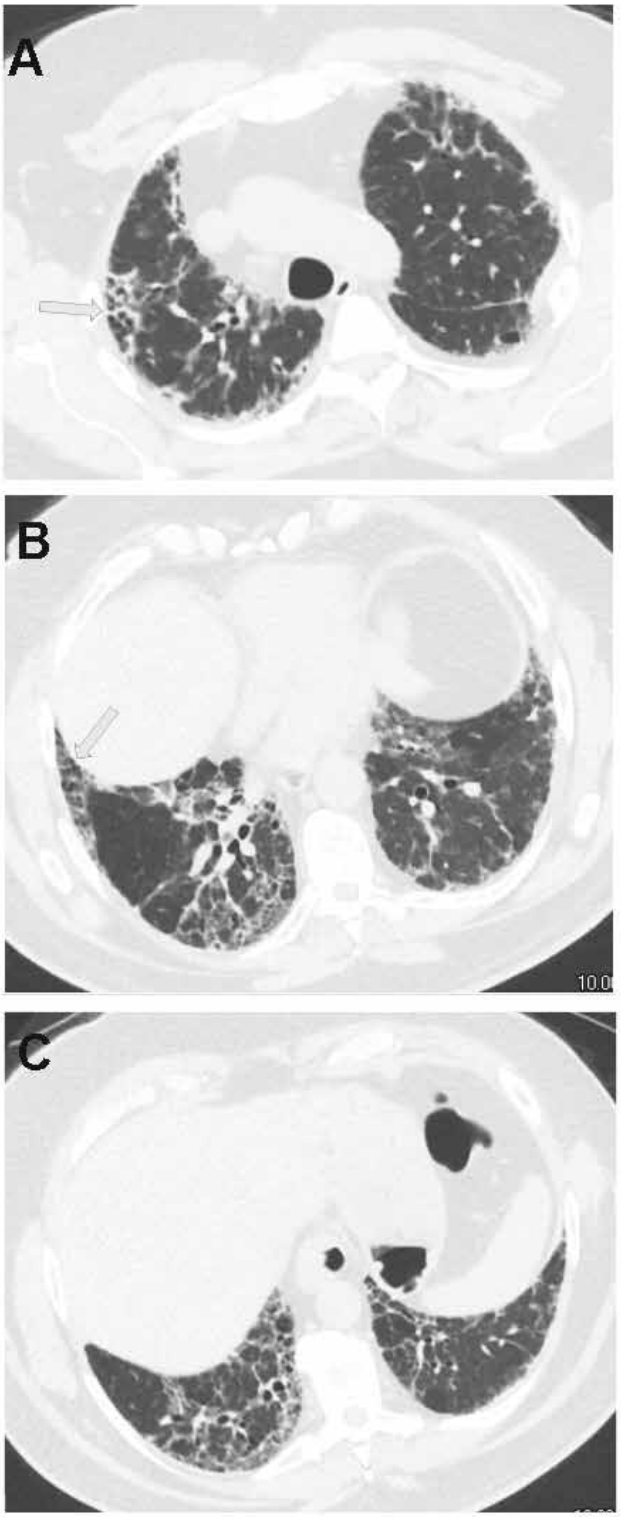

Figure 3. Axial HRCT scans at follow up from a patient with RA-ILD at the level of the aortic arch (A), right inferior pulmonary vein ostium (B), and just above the hemidiaphragms (C). The fibrosis has clearly progressed with worsening of the peripheral reticulation and traction bronchiectasis/bronchioloectasis. Honeycombing (arrows) is present. This is a UIP pattern of lung injury.

A case of anti-synthetase syndrome with myositis and ILD

A 58-year-old woman presented to our tertiary referral center with recurrent pneumonia. She denied any respiratory symptoms until six months prior to presentation when she developed pneumonia. She was treated with antibiotics and steroids and her symptoms improved until steroids were discontinued, at which time she developed recurrent cough and dyspnea. PFTs showed an FVC of 1.2 L (33% predicted), FEV_1 of 1.01 L (36% predicted) and FEV_1/FVC ratio of 84%. She was hospitalized several times (outside our center) and intubated for nine days three months after her first presentation for respiratory failure, which was thought to be secondary to pneumonia. COVID-19 testing was negative and bronchoalveolar lavage was negative for malignancy and infection. A transbronchial biopsy was not performed. The chest CT from the outside facility at the time of the respiratory failure showed multifocal ground glass and consolidative opacities that were reported as concerning for multifocal infection (Figure 7). An echocardiogram showed a normal LVEF and a right ventricular systolic pressure of 34 mmHg. She was a lifelong non-smoker and had no mold or feather exposures, but she lived on a pasture on which hay is baled, in a town with an abundance of cotton and peanut farms. Her family history is unknown, as she was adopted. She had neuropathy of unknown etiology that started a few years prior.

Laboratory tests outside our center showed a creatine kinase of 4079 U/L, aldolase of 41 U/L, a positive anti-Jo-1 antibody and positive anti-Ro 52kD at 130. Based on these data, the patient was diagnosed with anti-synthetase syndrome with myositis and ILD. Prednisone, which she had been on after her most recent hospitalization, was increased from 40 mg daily to 60 mg daily and mycophenolate mofetil was initiated at 500 mg twice daily. She

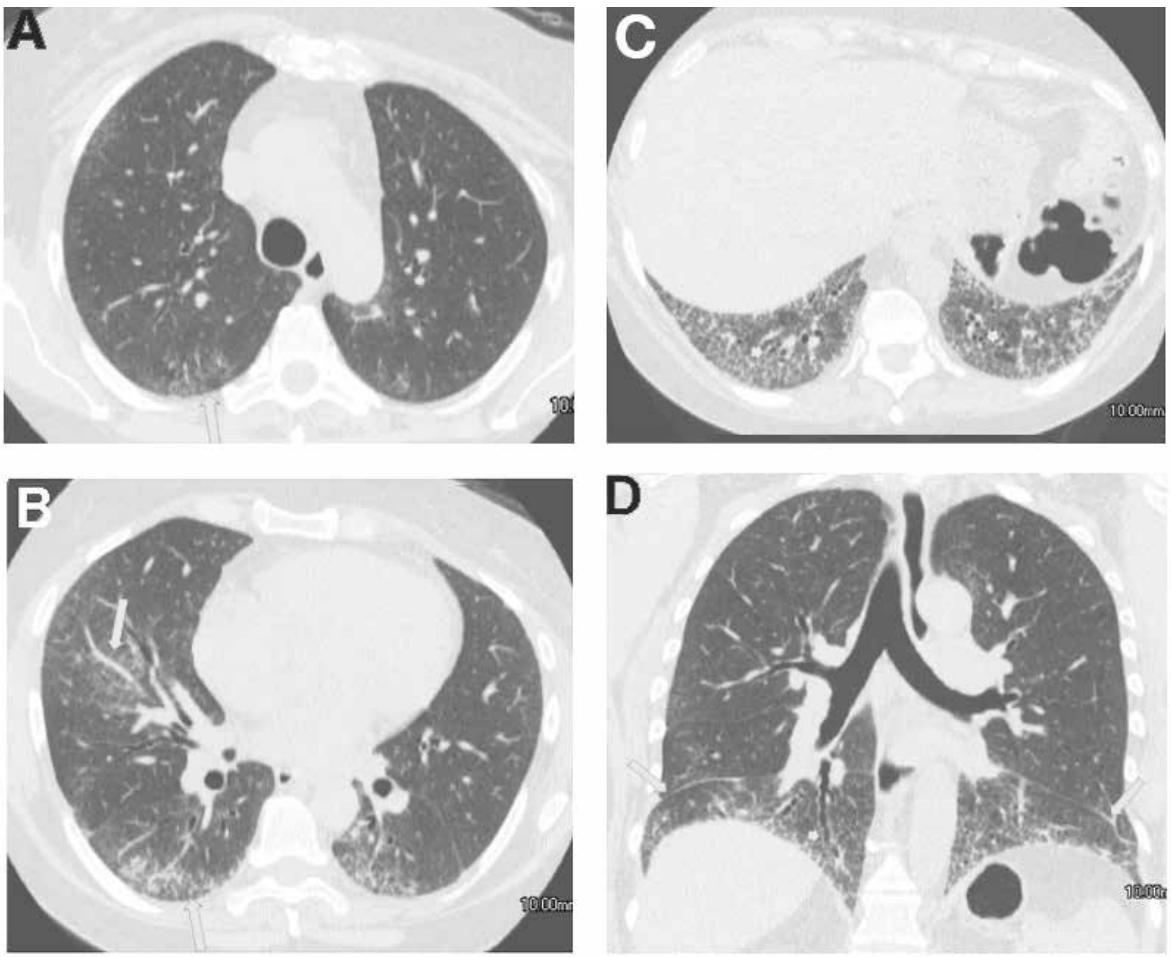

Figure 4. HRCT images at presentation in a patient with SSc-ILD. Axial image at the level of the aortic arch (A), axial image at the left inferior pulmonary vein ostium (B), axial image just above the hemidiaphragms (C), and coronal image (D) demonstrating the craniocaudal distribution of disease. Note the ground glass densities (arrows in A and B) with mild involvement of the upper lobes but progressively more severe involvement towards the bases. Extensive reticulation is seen in the bases with mild traction bronchiectasis/bronchioloectasis (arrowheads in C). Sparing of the immediate subpleural lung is best seen posteriorly on the right in B. Basilar predominant ground glass densities with traction bronchiectasis and subpleural sparing is typical of an NSIP pattern of lung injury. In the coronal HRCT image, unlike a UIP pattern of lung injury, NSIP shows a more homogenous basilar predominance and does not extend up the lateral sidewall. Note the volume loss characterized by the downward fissural displacement (arrows in D) as well as the traction bronchiectasis (arrowhead in D).

was started on trimethoprim/sulfamethoxazole for pneumocystis jiroveci pneumonia (PJP) prophylaxis.

Since her prolonged hospitalization with intubation, she maintained a supplemental oxygen requirement (2-3 L/min) and experienced muscle weakness. She reported low grade fevers, dry mouth, hair loss and parasthesia but denied weight loss, night sweats, dry eyes, nasal or oral ulcers, or Raynaud's phenomenon. She reported occasional sinus drainage with associated cough. Dyspnea on exertion remained stable with no chest pain. She reported gastroesophageal reflux and occasional dysphagia to pills and some foods. She noted redness over the MCP joints and cuticles of the fingers and joint pain and swelling, which worsened when off prednisone.

On evaluation at our center, her physical examination was notable for dry mouth. Her heart rate was tachycardic but with regular rhythm. Lung examination was notable for crackles at the bases bilaterally. Musculoskeletal examination showed no swelling or tenderness of the joints. Neurologic examination was notable for a hip flexor strength of 4-/5 and ability to stand on her own from a chair, which she noted was an improvement from the previous week, and upper extremity strength of 4+/5. Skin examination was pertinent for erythema of the cuticles bilaterally and at the distal tips of the fingernails.

In a multidisciplinary approach between pulmonary and rheumatology, mycophenolate mofetil was increased to 1000 mg twice daily and her respiratory status was reassessed. Creatine kinase level improved from 971 to 338 U/L. Prednisone was reduced from 60 mg daily to 50 mg daily, but the patient had worsening respiratory symptoms and worsening muscle weakness and tenderness, so the dose was increased back to 60 mg daily. As no notable improvement in respiratory status was observed with high doses of steroids plus mycophenolate mofetil over approximately six weeks and prednisone could not be tapered, alternative treatment options were explored. It was decided to add rituximab and increase the mycophenolate mofetil dose to 1500 mg twice daily until the rituximab infusion was initiated. The patient underwent infusion of rituximab-pvvr (a biosimilar to rituximab) (1000 mg x 2 doses, 2 weeks apart) and mycophenolate mofetil was decreased to 1000 mg twice daily, with a plan to decrease to 500 mg twice daily. The patient was able to decrease the prednisone dose to 40 mg daily and then to 25 mg daily three months after the rituximab-pvvr infusion. She was also started on alendronate for prevention of glucocorticoid-induced osteoporosis. Three months after rituximab-pvvr infusion, the patient's oxygen requirement had reduced to 2 L/min, mainly on exertion, with no flares, improvement in muscle pain, and 5/5 muscle strength on physical examination. The patient developed varicella zoster infection two and a half months after rituximab-pvvr infusion and was treated with anti-viral therapy. One year after presentation to our center, the patient was able to wean off oxygen and had 5/5 muscle strength in the upper and lower extremities. Her muscle enzymes normalized. She continues anti-CD20 therapy every six months and has been able to taper off mycophenolate mofetil and corticosteroids.

Discussion and Conclusion

ILD is a common manifestation of autoimmune diseases but its diagnosis in clinical practice is often delayed due to multiple factors. While PFTs can be utilized as a screening tool in some instances, diagnosis of ILD requires HRCT with inspiratory and expiratory views. All three of our ILD cases were diagnosed based on a compilation of clinical presentation, exposure history, physical exam, serologies and HRCT findings following MDD. Multiple studies have shown the utility of MDD to improve diagnostic accuracy for ILD and MDD has been endorsed in international consensus guidelines for the diagnosis of ILD [21]. In some cases, evaluation of an HRCT scan, laboratory data and clinical features do not enable a definite diagnosis of ILD to be made. Dynamic discussion among pulmonologists, radiologists, pathologists and rheumatologists is important to decide whether bronchoalveolar lavage or surgical lung biopsy is warranted to provide additional information [21-23]. The potential benefit of a surgical lung biopsy in confirming a diagnosis should be weighed against the risk of mortality due to the procedure [24-26]. Transbronchial lung cryobiopsy may be preferred to surgical lung biopsy at centers with the appropriate expertise [21].

In this report, the cases with RA-ILD and anti-synthetase syndrome with myositis and ILD had CT scans showing evidence of ILD before their diagnosis of autoimmune disease was confirmed. This demonstrates that, just as it is important that patients with autoimmune diseases are evaluated for ILD, patients with ILD should be evaluated for autoimmune disease. A study of 114 patients referred to an ILD clinic found that 15% of patients were diagnosed with a CTD following evaluation for ILD [27]. A recent analysis of US insurance claims data found that about 5% of patients with SSc had claims for ILD >1 year prior to a claim for SSc [28].

Decisions on how to treat ILDs other than IPF can be challenging and ideally should be based on MDD [26,29]. Patients with autoimmune disease-related ILDs often respond well to immunosuppressants, at least initially. The practice for management of the different autoimmune disease-related ILDs varies across centers, with clinical decisions influenced mainly by the findings of Scleroderma Lung Studies I and II, conducted in patients with SSc-ILD [5,6]. However, some patients, such as our patient with anti-synthetase syndrome, do not respond to mycophenolate mofetil or azathioprine and require escalation to rituximab or cyclophosphamide. While previous practices were based on small retrospective studies and clinical experience, recently published data from the RECITAL and DESIRES trials now support the use of these medications in patients with autoimmune disease-related ILDs [17,30]. Among patients with progressive autoimmune disease-related ILD, rituximab and cyclophosphamide were effective in

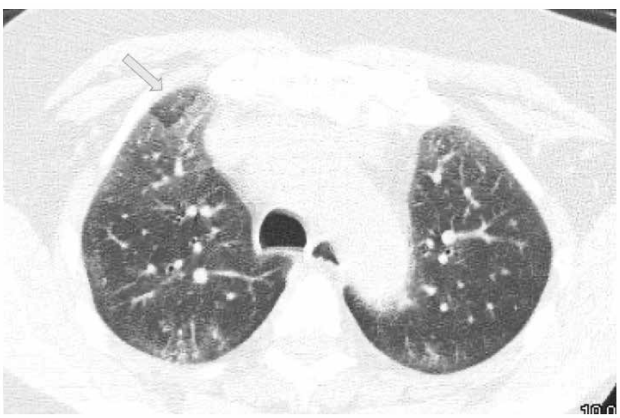

Figure 5. Prone expiratory HRCT image at presentation in a patient with SSc-ILD. Image demonstrates no significant air trapping (diffuse and bilateral involving three or more lobes). Mild lobular air trapping (arrow) is seen in the anterior right upper lobe. This patient was imaged in the prone position and the anterior lungs are dependent. Isolated lobular air trapping in dependent portions of the lung is common and should be considered physiologic and not indicative of significant small airways disease.

improving lung function; rituximab is better tolerated in this patient population [17]. We decided to use an approach that has not been described in the literature and switched to rituximab-pvvr, a biosimilar. This enabled a reduction in corticosteroid dose and led to a reduction in creatine kinase, consistent with previous studies [9,11]. Our patient was anti-Ro-52kD-positive, an autoantibody profile that has been shown to respond better to rituximab than to other immunosuppressants [31]. One of the main complications of combination immunosuppression and anti-CD20 therapy is infection, including PJP [11,31]. Our patient was given trimethoprim/sulfamethoxazole for PJP prophylaxis, but nonetheless developed varicella zoster infection. Clinicians should be mindful of PJP prophylaxis and administration of vaccines, including those for influenza and COVID-19, before initiation of anti-CD20 therapy and immunosuppression.

Unfortunately, some patients with progressive ILD continue to progress despite treatment. Guidelines recently published by an international group of pulmonology societies provided criteria for progressive pulmonary fibrosis in patients with ILDs other than IPF, based on worsening of symptoms, radiological findings, and lung function [21]. As demonstrated by all our cases, regular follow up of patients with fibrosing ILDs is important to enable prompt detection of progression of ILD or worsening of other manifestations of autoimmune disease or comorbidities so that changes to therapy can be implemented in a timely manner [26,32]. Equally important is an understanding of the risk factors for ILD progression in this patient population and having a proactive approach. Older age, male sex, and lower lung function are associated with a more progressive phenotype [33,34]. Patients with RA-ILD who have a UIP pattern on HRCT have been shown to have a worse prognosis than patients with a an NSIP pattern [35,36].

The INBUILD trial enrolled patients with fibrosing ILDs other

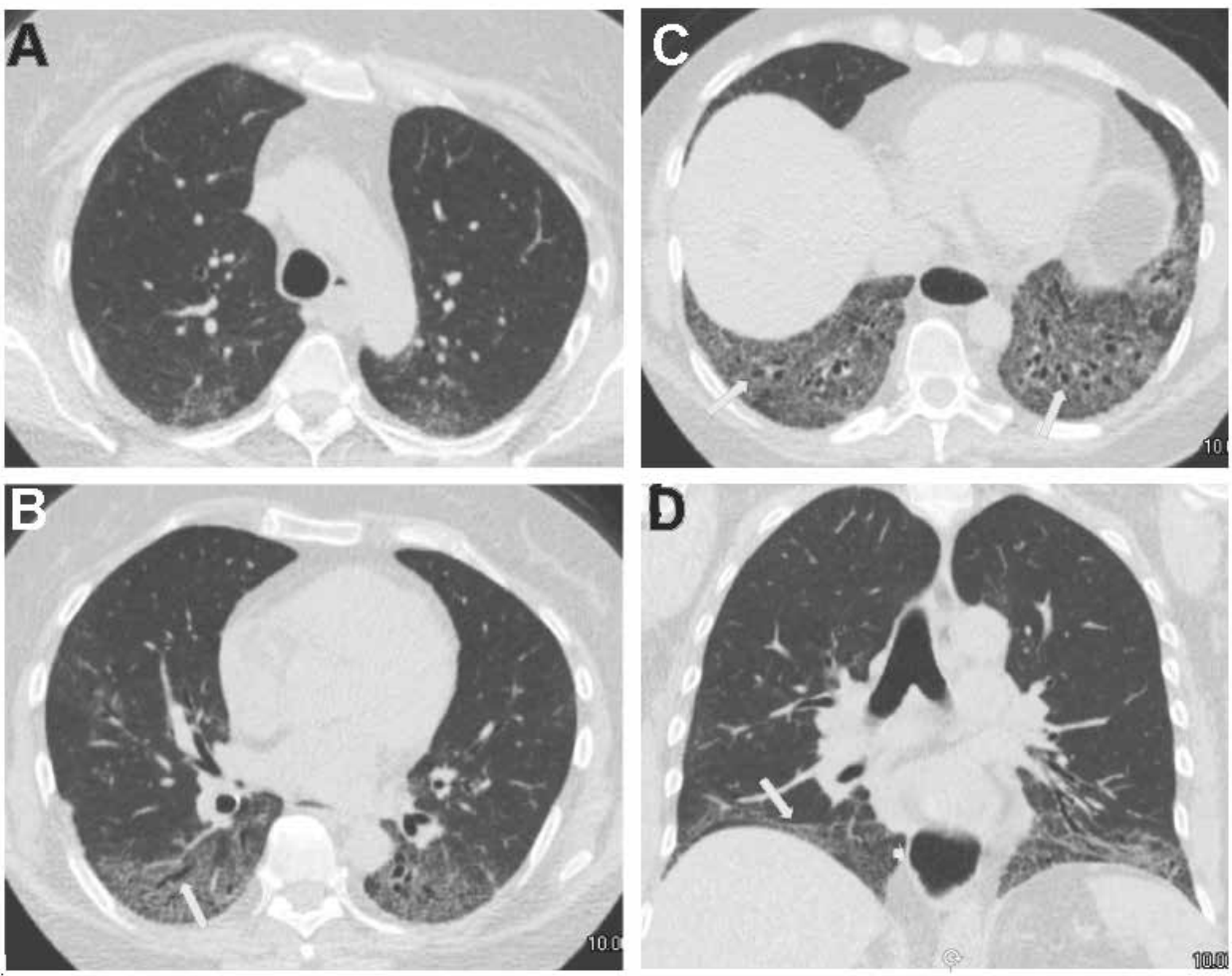

Figure 6. HRCT scans at follow up from a patient with SSc-ILD. Axial image at the level of the aortic arch (A), axial image at the left inferior pulmonary vein ostium (B), axial image just above the hemidiaphragms (C), and coronal image (D). The ground glass densities in the upper lobes in A have worsened modestly. Imaging through the mid and lower lungs in B and C shows clear progression of the basilar predominant ground glass density and reticulation. Traction bronchiectasis/bronchiolectasis has substantially worsened (arrows in C), compatible with fibrotic NSIP. Note the subpleural sparing is still evident posteriorly in B and C. Coronal image shows that basilar predominant ground glass opacities, reticulation, and traction bronchiectasis have worsened. The lower lobe volume loss has clearly progressed with marked downward displacement of the right major fissure (arrow in D). Note the dilated esophagus (arrowhead in D) typical of SSc.

than IPF who had shown progression of pulmonary fibrosis based on worsening of FVC, symptoms, or fibrotic abnormalities on HRCT within the previous 24 months, despite treatment in clinical practice [20]. In this patient population, nintedanib slowed the decline in FVC over 52 weeks, with no evidence of a differential treatment effect across diagnostic groups [20,37]. The subgroup of patients with autoimmune disease-related ILDs showed marked progression of ILD over 52 weeks [38], supporting the use of nintedanib in such patients. While the use of immunosuppression was restricted in the INBUILD trial, in the real world, combination therapy with immunosuppressive and antifibrotic agents is commonly used. Stable mycophenolate was allowed as background therapy in the SENSCIS trial [18].

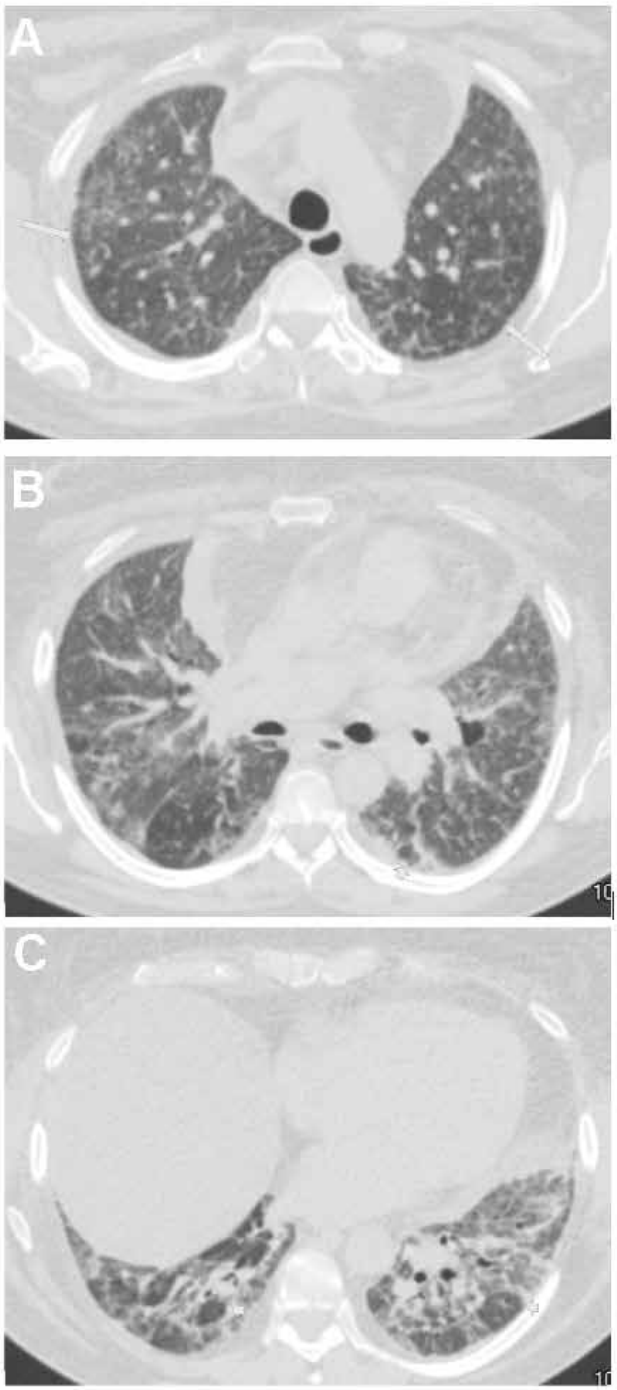

Figure 7. Axial HRCT images from a patient with anti-synthetase syndrome with myositis and ILD at the level of the aortic arch (A), below the carina (B), and just above the hemidiaphragms (C). Diffuse ground glass densities are present with areas of subpleural sparing (arrows) suggesting an NSIP pattern of lung injury. In the mid and lower lungs, more consolidative areas are noted, as well as areas of perilobular consolidation, suggesting an organizing pneumonia pattern of lung injury (arrowheads).

There is a grey area in determination of immunosuppression escalation versus addition of antifibrotic therapy in the management of progressive autoimmune disease-related ILDs. Inflammatory and fibrosing parenchymal abnormalities can influence clinical decisions. Ground glass opacifications are usually considered to represent a higher degree of cellularity and suggest that the disease is potentially more responsive to immunosuppression compared to the presence of fibrotic disease where antifibrotic therapies may be more effective. Other factors to take into consideration include the rate of disease progression, severity of lung disease, underlying autoimmune disease and extra-pulmonary symptoms, radiographic and histopathologic patterns, age, and ability to comply with therapy and monitoring [39-41]. As in our patient with SSc, when making therapeutic decisions, consideration should be given to the inflammatory versus fibrotic pattern on HRCT, extra-pulmonary symptoms and tolerability of therapies. For patients who progress despite pharmacological therapy, lung transplant should be considered [42]. Lung transplant may provide benefits on quality of life as well on survival [43]. Our first case, a patient with progressive fibrosing RA-ILD, did well after a lung transplant.

In conclusion, the diagnosis and management of ILD in patients with autoimmune diseases may be challenging and a multidisciplinary approach is recommended. Regular monitoring of patients with autoimmune disease-related ILDs is important to enable therapy to be initiated or escalated promptly if there is progression of ILD or worsening of other manifestations of disease.

Acknowledgements

Editorial support was provided by Elizabeth Ng and Wendy Morris of FleishmanHillard, London, UK, which was contracted and funded by Boehringer Ingelheim Pharmaceuticals, Inc. Boehringer Ingelheim was given the opportunity to review the article for medical and scientific accuracy as well as intellectual property considerations.

Abbreviations

NSIP: non-specific interstitial pneumonia;
MDD: multidisciplinary discussion;
anti-CCP: anti-cyclic citrullinated peptide;
CT: computerized tomography;
CTD: connective tissue disease;
DLco: diffusion capacity of the lung for carbon monoxide;
FEV_1: forced expiratory volume in one second;
FVC: forced vital capacity;
GERD: gastroesophageal reflux disease;
HRCT: high-resolution computed tomography;
IL-6: interleukin-6;
ILD: interstitial lung disease;
IPF: idiopathic pulmonary fibrosis;
LVEF: left ventricular ejection fraction;
MCP: metacarpophalangeal;
PFT: pulmonary function test;

PJP: pneumocystis jiroveci pneumonia;
RA: rheumatoid arthritis;
RV: residual volume;
SSc: systemic sclerosis
TLC: total lung capacity
UIP: usual interstitial pneumonia.

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Received for publication:13 October 2022. Accepted for publication: 21 March 2022.

Multidisciplinary Respiratory Medicine 2023; 18:890
doi:10.4081/mrm.2023.890

Multidisciplinary Respiratory Medicine 2022; volume 17:884

CASE REPORT

A case of secondary pneumothorax due to multiple pulmonary metastases of granulosa cell tumor

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ABSTRACT

Introduction: Ovarian granulosa cell tumor is a relatively rare tumor that accounts for 2-5% of malignant ovarian tumors. This tumor progresses slowly and may recur late in life.
Case presentation: A 70-year-old woman was admitted to our hospital with a left secondary pneumothorax due to metastatic lung tumors of granulosa cell tumor. Reports of secondary pneumothorax due to granulosa cell tumor are rare. Thoracoscopic suturing and pleurodesis using talc were effective in the treatment of this pneumothorax.
Conclusions: We experienced a rare case of secondary pneumothorax due to multiple pulmonary metastases of granulosa cell tumor. It should be noted that pulmonary metastasis of granulosa cell tumor can lead to secondary pneumothorax.

Key words: Granulosa cell tumor; secondary pneumothorax; check valve; thoracoscopic talc poudrage.

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Contributions: All the authors made a substantive intellectual contribution, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: The authors declare that they have no competing interests, and all authors confirm accuracy.

Ethics approval: No ethical committee approval was required for this case report by the Department, because this article does not contain any studies with human participants or animals. Informed consent was obtained from the patient included in this study.

Consent for publication: The patient gave written consent to use her personal data for the publication of this case report and any accompanying images.

Introduction

An ovarian granulosa cell tumor is a relatively rare tumor that accounts for 2-5% of malignant ovarian tumors [1-4]. The main clinical characteristic of this tumor is its tendency for late recurrence [5-7]. Recurrence with pulmonary metastasis was observed in approximately only 2.5% of recurrent cases [5]. Moreover, it is extremely rare for granulosa cell tumors to cause secondary pneumothorax. Furthermore, the treatment of this secondary pneumothorax has not been clarified. A rare case of secondary pneumothorax due to multiple pulmonary metastases of granulosa cell tumor is reported, and its clinical characteristics are compared to those of three similar cases that have been previously reported.

Case presentation

A 70-year-old woman came to our hospital complaining of left chest pain. On chest computed tomography (CT), a left pneumothorax and multiple metastatic lung tumors were observed. Thirteen years earlier, she was diagnosed with adult granulosa cell tumor of the right ovary, pStage-IA, and surgery was performed. Nine years earlier, she had a recurrence, and multiple lung metastases were observed. An aromatase inhibitor that suppresses endogenous estrogens was started four years earlier. She had a history of osteoarthritis of the knee. She had no smoking history. On admission, SpO_2 was 97% (room air), and breath sounds were attenuated on the left. Blood cell counts and biochemical tests showed no abnormal findings and no elevation of tumor markers including estradiol. The level of CA125 was 15.1 U/ml. A preoperative CT scan 13 years earlier showed a large ovarian tumor in the pelvis. The most recent ^{18}F-fluoro-deoxy-glucose (^{18}F-FDG) positron emission tomography CT (PET-CT) showed no evidence of recurrence in the pelvis. When pneumothorax appeared, collapse was stronger in the left upper lobe than in the left lower lobe. Therefore, the metastatic lesion located just below the pleura in the upper lobe was considered to be the lesion responsible for the pneumothorax.

After hospitalization, the pneumothorax was improved by left thoracic drainage. The patient was discharged without reappearance of the pneumothorax. After discharge from the hospital, mild recurrence of pneumothorax was observed on chest X-ray, but it resolved spontaneously without requiring re-drainage. After 6 months of outpatient follow up, the patient re-developed a left pneumothorax (Figure 1). Thoracic drainage was performed again, and the pneumothorax improved. However, since this left pneumothorax was the second one, surgical treatment was selected. Thoracoscopic suturing and pleurodesis using talc were performed in the upper lobe of the left lung. A leak test showed air leakage from the nodule at the interlobar margin of the lateral left upper lobe, which was speculated to be the responsible lesion (Figure 1 A,D). Two nodules in the apex of the left upper lobe were resected for histopathological examination (Figure 1 B,C,E,F). On pathology, a diffuse growing tumor composed of monotonous spindle cells that was consistent with metastasis of granulosa cell tumor was seen (Figure 2).

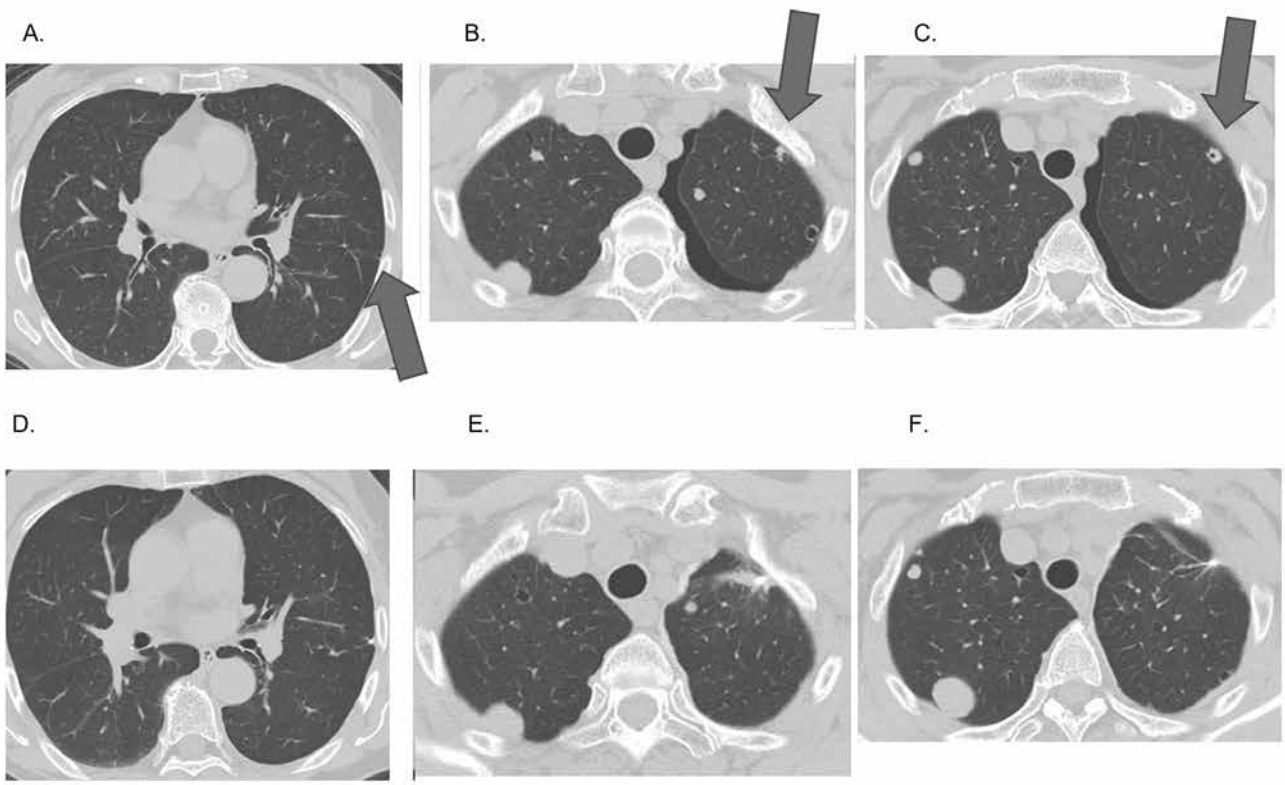

Figure 1. Chest CT findings before and after video-assisted thoracoscopic (VATS) surgery. A) The arrow shows the nodule with a cavity at the interlobar margin of the lateral left upper lobe, which was thought to be the responsible lesion. B,C) Pneumothorax is identified in the left lung; the arrow shows the nodules that were resected for histopathological examination. D) CT image of the left upper lobe after thoracoscopic suturing. E,F) CT images of the left upper lobe after video-assisted thoracoscopic biopsy.

Despite the absence of a smoking history, emphysematous changes were observed around the tumor. After this surgical treatment, the pneumothorax has been cured without recurrence.

Discussion and Conclusions

A rare case of secondary pneumothorax due to multiple pulmonary metastases of granulosa cell tumor was described. Pulmonary metastasis of granulosa cell tumor is rare, and there are few reports of secondary pneumothorax due to this tumor. To the best of our knowledge, there have been three previous reports of granulosa cell tumor with secondary pneumothorax [8-10]. The cause of the development of secondary pneumothorax varied from case to case (Table 1). Two cases developed secondary pneumothorax after chemotherapy or hormonal therapy for granulosa cell tumor. In the present case, the patient also had a secondary pneumothorax after hormonal therapy; it was assumed that the pneumothorax was caused by the shrinkage of a metastatic lung tumor that was located just below the pleura due to the hormonal therapy.

The incidence of secondary pneumothorax in metastatic lung tumors is about 1-2% of all pneumothoraces, and sarcoma, especially osteosarcoma, is the most common malignant tumor causing pneumothorax, at approximately 31.4% [11]. Several mechanisms have been proposed for the development of pneumothorax associated with metastatic lung tumors. Stein et al. reported that tumor cells that metastasize just below the pleura become necrotic due to angiogenesis during growth and introduction of chemotherapy, leading to pneumothorax when the pleura fails [12]. In fact, there have been reports of secondary pneumothorax after or during chemotherapy for metastatic lung tumors, and most of these cases were histopathologically attributed to pleural disruption due to necrosis of tumor cells just below the pleura [12-14]. Other reports suggest that the check valve mechanism of tumor infiltration into the bronchi causes alveolar hyperinflation and rupture [15], or that pneumothorax occurs as a result of tumor cells infiltrating the walls of existing lung cysts [16]. In the present case, the detailed mechanism was unknown, but two mechanisms were hypothesized. First, as described above, hormonal therapy caused necrosis of the metastatic tumor just below the pleura, resulting in pneumothorax. Second, a metastatic tumor located just below the pleura grew and obstructed the bronchi, causing a check valve. The check valve caused compensatory hyperinflation of the alveoli, leading to rupture and pneumothorax. The present patient had no history of smoking and no emphysema on chest CT. Therefore, the emphysematous changes around the tumor in the pathological findings might indicate the effect of the check valve, although the details were not clear [17-19].

There is a significant rate of recurrence of both primary pneumothorax and secondary pneumothorax [20]. In fact, in the present case, the patient had repeated episodes of pneumothorax of the left lung. Therefore, efforts to reduce recurrence by instilling various sclerosants *via* a chest drain, video-assisted thoracoscopic (VATS) surgery, or open surgery are often attempted [20]. In particular, thoracoscopic talc poudrage has been used successfully in secondary pneumothorax [20,21]. Lee *et al*. reported that thoracoscopic talc poudrage was effective for pneumothorax prevention and can be performed with acceptable mortality in patients with advanced COPD [21]. In addition, a meta-analysis of the success rates of talc pleurodesis in the treatment of pneumothorax has shown an overall success rate of 91% [22]. In the present case, thoracoscopic talc poudrage was also effective for repeated episodes of pneumothorax. Moreover, it was possible to identify the responsible lesion by performing thoracoscopy. Since the metastatic lung tumors could worsen, and the pneumothorax could recur in the future, it was considered reasonable to perform thoracoscopic talc poudrage to prevent pneumothorax. In the previous 3 reports, chest tube insertion was performed in 2 cases (Table 1). A case of secondary pneumothorax due to multiple pulmonary metastases of granulosa cell tumor was presented. It should be noted that pulmonary metastasis of granulosa cell tumor can lead to secondary pneumothorax. In addition, thoracoscopic talc pleurodesis could effectively treat this kind of pneumothorax caused by a metastatic lung tumor.

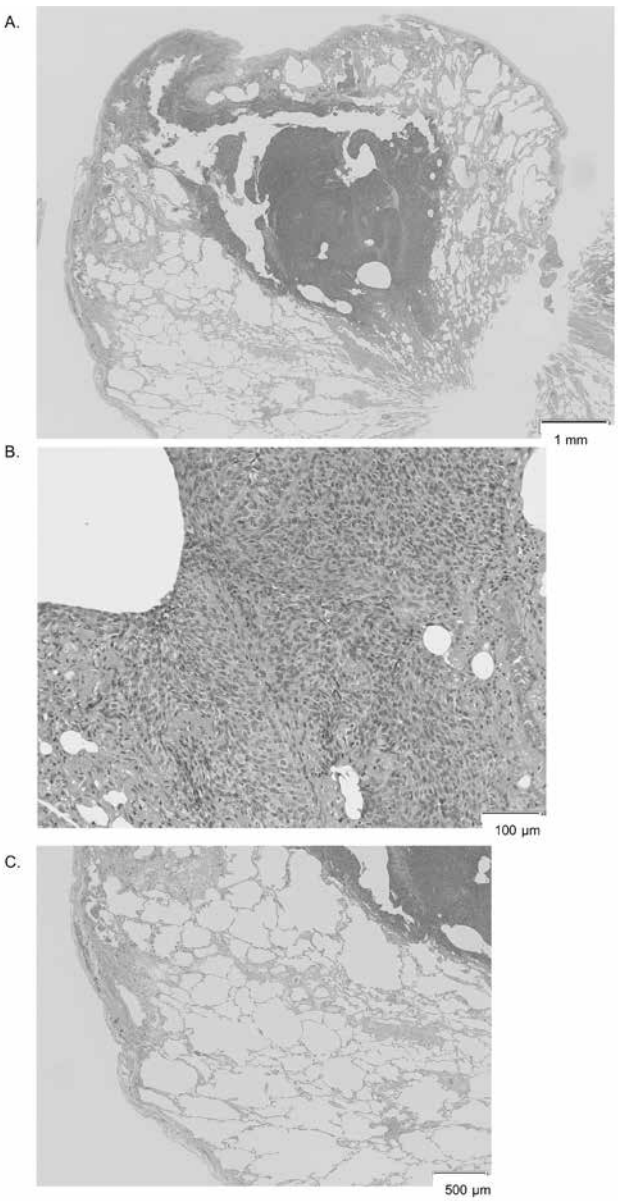

Figure 2. Pathological findings of specimens obtained by video-assisted thoracoscopic (VATS) surgery. A) Neoplastic lesions are found in the emphysematous lesions (Hematoxylin & Eosin stain, original magnification x 20). B) High-power micrograph of tumor showing a sarcomatoid pattern of monotonous spindle tumor cells; some cells show nuclear grooves (Hematoxylin & Eosin stain, original magnification x 200). C) Emphysematous changes are observed around the tumor (Hematoxylin & Eosin stain, original magnification x 40).

Table 1. Comparison of cases with secondary pneumothorax due to multiple pulmonary metastases of granulosa cell tumor.

Reference	Age at the onset of pneumothorax (y)	Time from GCT diagnosis to the onset of pneumothorax (y)	Treatment of GCT at the onset of pneumothorax	Treatment for pneumothorax
Schulman *et al.* [8]	19	1	Chemotherapy	Chest tube
Davidson *et al.* [9]	67	17	No treatment	Median sternotomy and bilateral pleurodesis
Alkhatib *et al.* [10]	84	27	Hormonal therapy	Chest tube
Present case	69	13	Hormonal therapy	Chest tube, thoracoscopic talc poudrage

GCT, granulosa cell tumor.

Abbreviations

GCT, granulosa cell tumor
PET-CT, ^{18}F-fluoro-deoxy-glucose (^{18}F-FDG) positron emission tomography CT.

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Received for publication: 22 September 2022. Accepted for publication: 8 November 2022.

Multidisciplinary Respiratory Medicine 2022; 17:884
doi:10.4081/mrm.2022.884

Efficacia e sicurezza di un lisato batterico nella prevenzione delle infezioni respiratorie ricorrenti: review delle evidenze e meta-analisi

Gianfranco Sevieri[1]*, Rigoletta Vincenti[2]

RIASSUNTO
Le infezioni delle vie respiratorie (RTIs) rappresentano un problema rilevante ed emergente in tutto il mondo, perché rappresentano una delle cause più comuni di morte.
Le malattie respiratorie sono inoltre responsabili della riduzione della qualità di vita (QOL) dei pazienti, con un impatto rilevante sia nella pratica clinica che in termini di costi.
Una strategia per la gestione e il trattamento delle infezioni respiratorie si esplica nell'uso di lisati batterici introdotti negli anni '70 in qualità di "vaccini orali".
A tal proposito, Buccalin® può rappresentare una sfida terapeutica per la profilassi delle infezioni ricorrenti delle vie respiratorie.
L'obiettivo di questo studio è quello di fornire uno scenario esaustivo della letteratura sui lisati batterici, con un'enfasi specifica per Buccalin®, e una metanalisi focalizzata sulla capacità di questo medicinale di ridurre l'incidenza delle infezioni respiratorie per i differenti settings clinici.

Parole chiave
Buccalin®, QOL, RTIs.

INTRODUZIONE

Infezioni dell'apparato respiratorio: un importante problema clinico e sociale (prospettive epidemiologiche e impatto sulla salute pubblica)

Le infezioni virali e batteriche del tratto respiratorio sono una delle principali cause di morbilità e mortalità nel mondo [1-5].

Dati recenti suggeriscono come la coinfezione sostenuta da vari patogeni, rispetto a infezioni singole, sia la responsabile di episodi ricorrenti, di maggiore durata e talora gravi [5].

Infatti, accade di frequente che un paziente si presenti al clinico con una storia di infezione (presumibilmente virale) delle alte vie respiratorie (es. congestione nasale, rinorrea, faringodinia) che può inizialmente migliorare, ma poi peggiorare dopo pochi giorni manifestandosi con sintomi che fanno sospettare un'infezione batterica (tosse produttiva, escreato più o meno purulento, cefalea, febbre) [5].

È noto che i virus possano predisporre le vie respiratorie alla sovrainfezione batterica attraverso differenti meccanismi:

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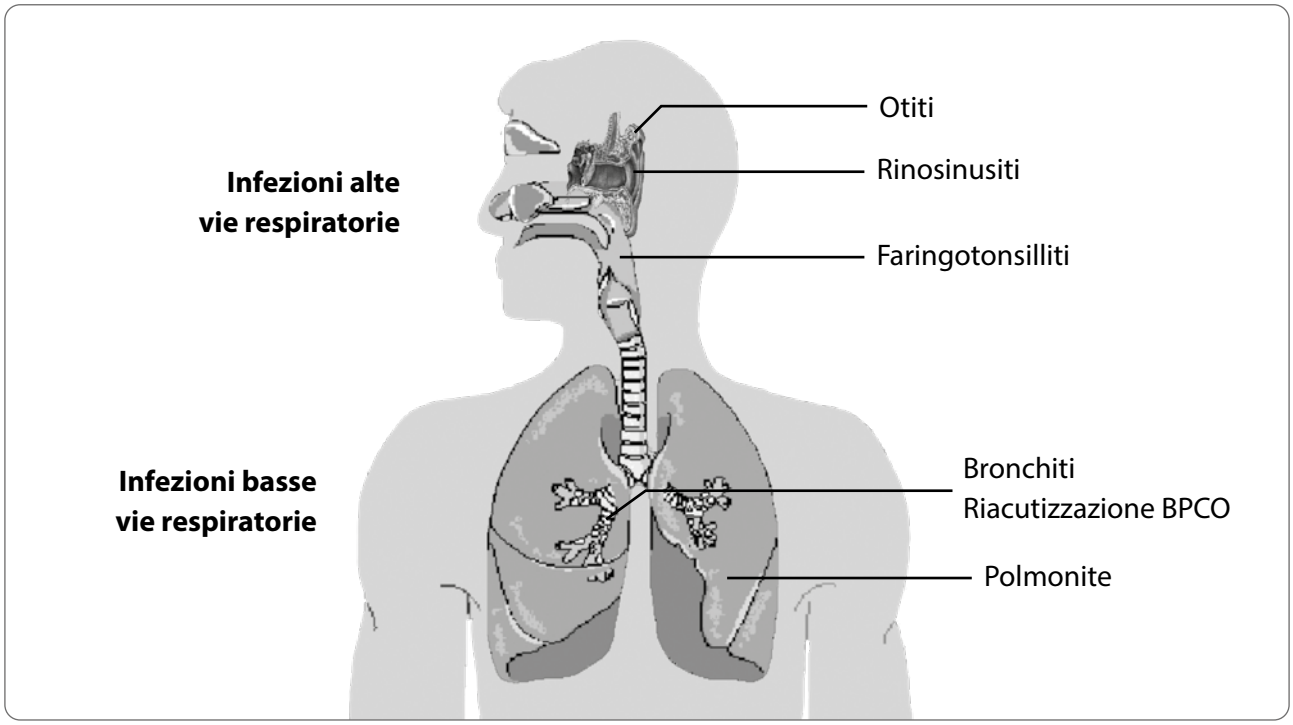

Figura 1 Le infezioni respiratorie possono riguardare le basse o le alte vie respiratorie. Tratto da [6] mod.

- effetto citopatico e ciliostatico sull'epitelio respiratorio che favorisce l'adesività dei batteri che colonizzano le vie aeree e la loro penetrazione nella sottomucosa bronchiale dove inizierà l'infezione;
- rilascio di mediatori flogogeni con disregolazione della risposta immunitaria innata e adattativa [6].

Queste alterazioni patomorfologiche spiegano perché le percentuali di complicanze batteriche siano più alte durante le stagioni in cui predominano virus respiratori compresi i vari tipi di influenza [7].

La risposta immune (innata e adattativa) sembra giocare un ruolo cruciale contro queste infezioni a diversa eziologia, attraverso la produzione e l'attivazione di specifici anticorpi [8].

Pertanto, è importante considerare la necessità di regolare in maniera efficace il sistema immunitario e i concomitanti meccanismi infiammatori con l'obiettivo di minimizzare il danno alle vie respiratorie, garantendo al tempo stesso un'adeguata protezione contro una varietà di agenti virali e batterici che provocano l'infezione [9].

Raffreddore e influenza

Il raffreddore comune "coriza o rinite da freddo" è la più frequente patologia che comporta assenza dal lavoro o dalla scuola e costi per la sanità pubblica sia in pediatria che in medicina generale [10].

Come il raffreddore anche l'influenza colpisce, ogni anno, a diversa intensità, gran parte della popolazione [11].

Dai dati epidemiologici si evince che un bambino, nei primi dieci anni, ha da 4 a 8 episodi in un anno, con una maggior incidenza nei primi 3 anni se frequenta l'asilo nido [10].

In bambini in età prescolare, invece, l'incidenza media del raffreddore varia da 5 a 7 episodi l'anno, anche se va considerato che un 10-15% dei bambini raggiunge 12 episodi annui [11].

L'incidenza decresce con l'età: in età adulta, infatti, si riscontrano 2- 3 episodi l'anno [11].

Nei climi temperati il raffreddore può insorgere tutto l'anno, con un'incidenza ridotta durante i mesi estivi.

La "stagione dei virus respiratori" nell'emisfero nord inizia con un aumento delle infezioni in agosto/ settembre e termina dopo un picco primaverile [11].

Sebbene i rinovirus continuino a circolare nei mesi invernali con incidenza più o meno alta, la stagione racchiusa tra questi picchi è caratterizzata spesso da episodi ricorrenti [11].

L'incidenza stagionale dei virus parainfluenzali solitamente presenta picchi nel tardo autunno e nella tarda primavera mentre RSV e influenza raggiungono picchi più alti tra dicembre e aprile [11].

Nei climi tropicali invece, il raffreddore è prevalente per tutto l'anno soprattutto in concomitanza con la stagione delle piogge [11].

Molto spesso nella pratica clinica è difficile distinguere tra raffreddore comune e influenza: infatti il quadro cli-

nico (specialmente in caso di influenza lieve o moderata) tende a sovrapporsi e una diagnosi eziologica non viene mai fatta, a meno che non si sottoponga il paziente a una identificazione del virus tramite Polymerase Chain Reaction (PCR) [11].

I rinovirus costituiscono l'eziologia più frequente del comune raffreddore (4 -50% secondo dati epidemiologici), mentre il virus influenzale con le sue varianti incide dal 25 al 30% [10-12].

Infezione virale: patogenesi

I virus, dopo avere degradato le tight junction (che svolgono funzione sigillante fra cellule adiacenti) dell'epitelio rinosinusale provocandone infiammazione e rendendolo più permeabile ad agenti esterni, si diffondono attraverso le secrezioni che dal naso scivolano lungo la parete posteriore della faringe fino alla laringe.

Il loro secondo bersaglio è l'epitelio tracheobronchiale dove i virus svolgono sia un'azione citopatica e ciliostatica che proteolitica sulle IgAs, anticorpi la cui funzione è impedire ai batteri di aderire alle mucose respiratorie.

Questi effetti indotti dai virus favoriscono l'adesione dei batteri che colonizzano le vie aeree inferiori generando bronchiti catarrali o polmoniti.

Va precisato, tuttavia, che il quadro clinico iniziale indotto dalla virosi si manifesta dopo un breve periodo di incubazione, con ostruzione nasale, rinorrea cefalea e faringodinia, e successivamente o contemporaneamente con una bronchite acuta i cui sintomi sono tosse scarsamente produttiva, febbricola, difficoltà a fare un respiro profondo.

Questi sintomi derivano dal rilascio di mediatori flogogeni in risposta all'infezione virale e, secondo le evidenze cliniche, l'infiammazione è più intensa nei neonati e nei bambini piccoli [10].

Non c'è una terapia specifica per il raffreddore: il trattamento è sintomatico ma nei bambini i rimedi terapeutici hanno prodotto scarsa efficacia sotto il profilo clinico [11].

Non è chiaro se questo sia dovuto, in questa popolazione, semplicemente alla difficoltà di valutare i sintomi soggettivi dei piccoli pazienti [11].

Sarebbe particolarmente utile, invece, un trattamento mirato a rafforzare le difese immunitarie.

Al contrario, studi condotti sulla popolazione adulta hanno dimostrato l'efficacia del trattamento indirizzato all'ostruzione nasale responsabile di rinorrea, cefalea e faringodinia [11].

I trattamenti abituali per i sintomi del raffreddore vertono sull'utilizzo di farmaci agonistici adrenergici (decongestionanti nasali), antistaminici per la gestione della rinorrea, antiinfiammatori non steroidei (FANS), ibuprofene e paracetamolo per i sintomi tipici dell'infiammazione come il mal di gola [11].

Recenti evidenze cliniche suggeriscono che l'influenza è spesso complicata da sovrinfezioni batteriche dovute a differenti ceppi patogeni [9].

I dati pubblicati evidenziano che le sovrinfezioni batteriche sono la complicanza più frequente di molte virosi respiratorie (Rhinovirus, Influenza A e B, Virus parainfluenza, Virus Respiratorio Sinciziale RSV, Coronavirus e Adenovirus) [9].

Questa associazione porta a un aumentato rischio di eventi acuti come le riacutizzazioni infettive che costellano il decorso naturale della BPCO.

La morbilità e la mortalità provocate da queste sovrainfezioni o dall'insorgenza di polmonite sono correlate spesso a fattori di rischio come l'età (infanzia e senescenza), la gravidanza, le comorbilità (malattie cardiovascolari, diabete, epatopatia cronica, insufficienza renale cronica allo stadio terminale, obesità) e un sistema immunitario compromesso.

Le riacutizzazioni infettive della BPCO sono contrassegnate da una recrudescenza dei sintomi respiratori abituali (aumento della tosse, produzione di escreato e dispnea).

Questi episodi, che costringono il paziente ad assumere più farmaci e a richiedere l'intervento del medico, comportano deterioramento della funzionalità respiratoria, aumentato rischio di morbilità e mortalità a breve e a lungo termine, peggioramento della qualità di vita, limitazione delle normali attività quotidiane.

Essi risultano inoltre responsabili di una percentuale significativa di visite mediche, accessi in Pronto Soccorso, ma in particolar modo, di ospedalizzazioni (durata media 10 giorni) che si rendono necessarie per quei pazienti con funzionalità respiratoria più compromessa e/o per il fallimento della terapia domiciliare, con importanti ripercussioni sulla spesa sanitaria.

I patogeni maggiormente isolati durante una riacutizzazione batterica sono *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* (Infernal trio) e in percentuale minore lo *Staphylococcus aureus*.

La polmonite

È noto che le cavità nasali e i seni paranasali sono la più grande "Riserva naturale" dello pneumococco (20-58% "bambini sani"; 5-10% negli adulti "sani": percentuali che raggiungono nei mesi invernali il 60%).

La coriza virale, infatti, produce fluidi contenenti mucine che rappresentano "*pabulum*" idoneo alla crescita di *Pneumococchi*.

Lo Pneumococco viene aspirato dal tratto naso faringeo nelle vie aeree inferiori dando luogo alla polmonite.

In alcuni casi può superare la barriera ematica quando le difese immunitarie sono compromesse e dar luogo alla Malattia Pneumococcica Invasiva (IPD: *Invasive Pneumococcal Disease*) con meningite e sepsi [13].

Evidenze scientifiche affermano che la polmonite pneumococcica è la complicanza più frequente del virus influenzale sia sul territorio che in soggetti ospedalizzati per influenza dove la prognosi è più severa con necessità di trasferimento in UTI e/ o mortalità.

I fattori di rischio che rendono più vulnerabili i pazienti sono: non avere effettuato vaccino antifluenzale, età ≥ 65 anni, residenza in RSA, un sistema immune compromesso, le comorbilità (BPCO, malattie cardiovascolari, diabete, epatopatie, insufficienza renale cronica).

Anche lo *Staphylococcus aureus* può essere il patogeno complicante l'influenza, come dimostrato in uno su 38.665 pazienti ospedalizzati per influenza, dove il patogeno era maggiormente isolato [14].

Inoltre, lo *Staphylococcus aureus* è un potenziale agente causale di polmoniti anche nei bambini come complicanza del virus influenzale.

La polmonite da *Staphylococcus aureus* è pericolosa perché può complicarsi con pneumatoceli, raccolte aeree di aspetto cistico, causate dall'infiammazione e in grado di determinare, con un meccanismo a valvola, la penetrazione di aria nel parenchima polmonare [13,15].

Lisati batterici nella profilassi delle infezioni respiratorie

I lisati batterici sono costituiti da una miscela di vari antigeni batterici secondo l'estratto considerato.

Le specie più spesso incluse sono: *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Streptococcus viridans*, *Streptococcus pyogenes*, *Klebsiella pneumoniae*, *Klebsiella ozaenae*, *Moraxella catarrhalis*, *Hemophilus influenzae* [16].

Il lisato batterico è un agente immunostimolante in grado di incrementare l'immunità nelle vie aeree superiori e inferiori attraverso la produzione di IgAs, mediante l'attivazione dei linfociti T Helper e dei Linfociti B [16].

Il sistema di difesa immunitaria possiede due distinti tipi di risposta: innata e adattativa.

L'immunità innata non è un meccanismo dissociato dall'immunità adattativa, ma contribuisce a stimolarla e a influenzarla tramite alcuni mediatori e segnali molecolari.

L'immunità adattativa, nota anche come immunità acquisita o immunità specifica, è una risposta immunitaria caratterizzata dal suo adattamento a ciascuna infezione, ed è generalmente più efficace e più specifica dell'immunità innata, seppure impieghi più tempo di quest'ultima per agire.

L'immunità adattativa si divide a sua volta in una immunità umorale e immunità cellulo-mediata.

Le cellule che intervengono nella risposta immunitaria innata sono linfociti NK, neutrofili, macrofagi e cellule dendritiche.

Queste cellule riconoscono tramite recettori situati sulla loro membrana esterna detti PRR (Patterns Recognition Receptors) i PAMPs (Pathogen Associated Molecular Patterns) che sono molecole o porzioni di molecole caratteristiche di alcuni patogeni (PAMPs: lipopolissaccaridi (LPS) espressi da molti batteri, oligosaccaridi delle membrane batteriche ricchi di mannosio e fucosio, acido teicoico (parete batterica dei Gram +) RNA virali a doppio filamento, peptidi, esclusivi dei batteri contenenti N-formilmetionina), ed essenziali per la sopravvivenza del patogeno stesso che non sono espressi dalle cellule dell'organismo, per cui vengono identificati come "non self" dalle cellule dell'immunità innata [6].

L'attivazione di questi recettori (PRR) presenti nelle cellule dell'immunità innata, mediante trasduzione del segnale, scatena una risposta effettrice (immunità acquisita) innescando la fagocitosi e il rilascio di citochine e chemochine [6].

Presentazione dell'antigene alle cellule immunitarie adattative dirette contro il patogeno specifico

Gli antigeni batterici sono processati dalle cellule dendritiche che li presentano ai linfociti T Helper consentendone la maturazione in TH1 e TH2.

I TH1 stimolano la produzione di IFNγ; i TH2 attivano i linfociti B con conseguente maturazione delle plasmacellule e secrezione di anticorpi specifici (IgAs).

Questi anticorpi che all'inizio sono monomeri, quando arrivano all'epitelio respiratorio attraverso il dotto toracico proveniente dall'intestino, si accoppiano e diventano dimeri.

Il pezzo che li unisce si chiama pezzo secretorio, prodotto dall'epitelio respiratorio.

Questi anticorpi si dispongono su tutto il tratto respiratorio modulando una ridotta penetrazione di virus e batteri, rendendo meno severa la patologia infettiva e allungando l'intervallo libero da episodi acuti (free interval).

La secrezione di IgAs diretti verso gli antigeni batterici (funzione di esclusione antigenica) ha un effetto positivo perché essi hanno la capacità di opsonizzare le cellule batteriche in modo da favorire la fagocitosi e la loro uccisione.

Tutti questi dati indicano che l'attivazione delle cellule dendritiche, l'attivazione specifica dei linfociti T e B e la conseguente produzione di IgA nella mucosa respiratoria specificamente diretti agli antigeni somministrati e in grado di opsonizzare i batteri, rappresentano il "vero effettore "della risposta immunitaria con conseguente effetto protettivo sulle infezioni ricorrenti delle vie respiratorie.

Occorre però ricordare che l'omeostasi del sistema immunitario è sempre regolata da una particolare sotto-

popolazione di linfociti, detti T-suppressor, specializzata nel frenare l'eccessiva attivazione.

Pertanto, in accordo con i dati pubblicati in letteratura, i lisati batterici possono essere considerati potenti induttori di una risposta immune a livello delle mucose respiratorie.

Le Figure 2, 3 e 4 mostrano come l'intero sistema immunitario si attivi quando incontra agenti patogeni che hanno superato le barriere anatomiche.

Alla luce delle considerazioni di cui sopra, si può presumere che i lisati batterici debbano essere considerati efficaci sia sui sintomi, riducendone gravità e durata, che sulla prevenzione di infezioni, anche ricorrenti, a diversa eziologia e con un buon profilo di tollerabilità [6].

Obiettivo di questo lavoro è raccogliere e analizzare i dati disponibili su efficacia, tollerabilità e sicurezza di Buccalin®, un lisato composto da ceppi inattivi di *Streptococcus pneumoniae I, II, III*, *Streptococcus agalactiae*, *Staphylococcus aureus*, *Haemophilus influenzae*, nella prevenzione delle infezioni ricorrenti respiratorie.

Le barriere anatomiche che ostacolano il passaggio dei patogeni

IMMUNITÀ INNATA	
CUTE	Gli strati più superficiali costituiti da cheratinociti morti. Nell'epidermide sboccano i dotti delle ghiandole sudoripare il cui secreto contiene IgA, urea e alcuni acidi grassi che, oltre a lubrificare la pelle, inibiscono la crescita batterica.
NASO	Produce un muco contenente acqua, ioni e mucine, lisozima, lattoferrina, **IgA**, **IgG**.
SANGUE	Numerose le proteine antimicrobiche: lattoferrina, lisozima, interferone, fibronectina, TNFa, IgA, IgE, IgG, IgM.

Figura 2 Barriere anatomiche che ostacolano il passaggio dei patogeni. Tratto da [6] mod.

Immunità innata: barriere anatomiche

IMMUNITÀ INNATA	
LACRIME	Numerose proteine antimicrobiche: lisozima, lattoferrina, lipocaina, IgA.
APPARATO GASTRO-ENTERICO	Ambiente sfavorevole: • basso pH (stomaco) • presenza di bile • succo pancreatico, ricchi di enzimi idrolitici

Figura 3 Immunità innata: barriere anatomiche. Tratto da [6] mod.

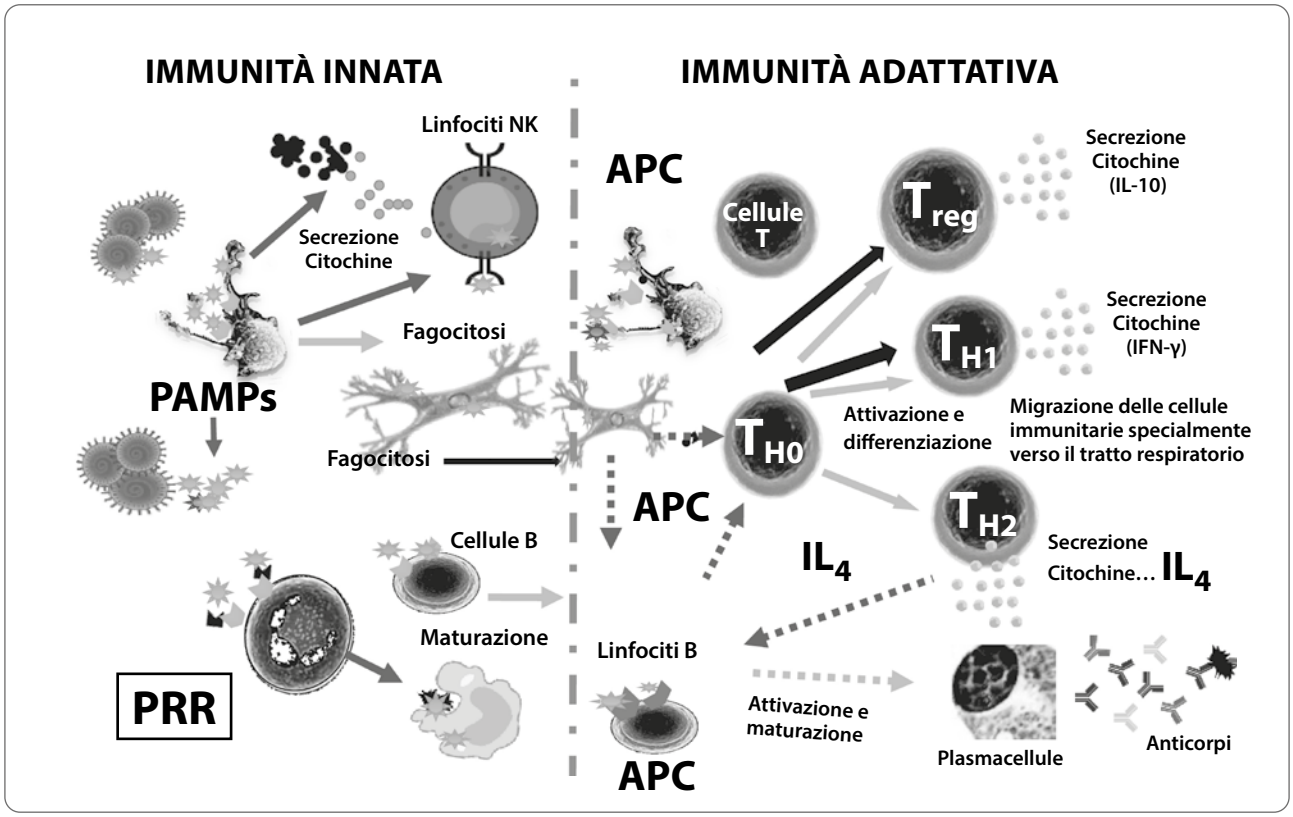

Figura 4 Immunità innata e immunità adattativa o acquisita. Tratto da [6] mod.

BUCCALIN®

Fonti di informazione

Le fonti riportate in questa review e metanalisi sono una selezione della letteratura clinica pubblicata (tutti i trials clinici comparativi e non comparativi disponibili).

Le aree esplorate su Buccalin® da studi pubblicati/report sono le seguenti:

- farmacodinamica primaria e secondaria / farmacocinetica;
- efficacia e sicurezza (Case reports);
- trials clinici randomizzati (RCTs);
- tutta la documentazione disponibile dall'archivio del Marketing Authorisation Holder (MAH).

Gli aggiornamenti sul profilo clinico di Buccalin® sono stati ottenuti mediante i seguenti database di farmacologia:

- AHFS (American Society of Health- System Pharmacists 2023);
- Martindale online (2023);
- The Medline and Embase databases, queried through STN/Karlsruhe.

La ricerca è stata eseguita nel maggio 2023 per un totale di 1.622 documenti pubblicati nel periodo 1954-2023.

Tra i 1.622 articoli, 54 sono stati considerati rilevanti e costituiscono la base di conoscenze per questa review.

Considerazioni generali: proprietà farmacodinamiche e farmacocinetiche

A partire dal 1970, i lisati batterici sono stati sviluppati e utilizzati con lo scopo di prevenire le infezioni respiratorie sia nella popolazione pediatrica che adulta [17].

Per quanto riguarda la farmacodinamica, il Buccalin® ha la capacità di attivare i meccanismi dell'immunità sia innata che acquisita [17].

Infatti, il sistema dell'immunità innata attraverso la produzione di citochine, chemochine, fattori di crescita è capace di attivare la risposta adattativa e promuovere l'attivazione di linfociti T e B fino alla produzione di IgAs [17].

I ceppi batterici contenuti in Buccalin®, somministrato per via orale, dopo essere state processati a livello intestinale, attivano le cellule immunitarie che conducono alla formazione di IgA nelle secrezioni della mucosa respiratoria.

Pertanto, l'immunostimolazione mucosale *per os* appare un approccio attrattivo, sebbene non sia alternativo alla vaccinazione sistemica per via parenterale contro i patogeni considerati.

L'immunostimolazione orale innesca la risposta immunitaria a livello delle mucose che coinvolgono sia il braccio cellulare che quello umorale del sistema immune [18].

La presenza di un meccanismo aspecifico e l'attivazione di un'immunità specifica mediante immunostimolazione orale aumenta notevolmente la resistenza alle infezioni respiratorie [19].

Uno dei più importanti meccanismi di azione della immunomodulazione orale è l'attivazione di agglomerati linfatici (placche del Peyer's) che occupano la lamina propria e la sottomucosa dell'ileo, dell'intestino tenue e vascolarizzate da un'estesa rete di capillari [18,19].

Dopo il contatto con l'antigene, linfociti mucosali attivati migrano ai linfonodi locali e poi ritornano attraverso la via linfatica e la circolazione ematica a tutte le mucose dove vengono secrete le IgA.

Le IgA secretorie sono gli anticorpi predominanti nelle secrezioni respiratorie ed esercitano un ruolo importante nell'immunità locale [18,19].

Tutto questo deriva dalla scoperta alla fine degli anni '60 di Bienenstock che definì come MALT (*Mucosal Associated Linphoid Tissue*) quella risposta immune che iniziando dal GALT (*Gut Associated Linphoid Tissue*) termina a livello del BALT (*Bronchial Associated Linphoid Tissue*).

Queste due componenti si parlano, nel senso che il tessuto linfatico presente nell'intestino amplifica, sotto stimolo di antigeni specifici orali, la risposta immunitaria del BALT attraverso la produzione di IgAs.

La dimostrazione deriva da un esperimento dove cavie il cui intestino era in condizione di "*germ free*" andavano incontro a infezioni ripetute e morte.

Questo lavoro finì con questa conclusione: "*dacci oggi il nostro germe quotidiano*".

Questo certifica che Buccalin®, avendo un forte potere immunogeno, è in grado di sostenere una potente risposta immunitaria rispetto ad altri composti che, anche se contenenti milioni di microorganismi (i nutraceutici), non riescono ad effettuare quella risposta immunitaria perché incapaci di esercitare un effetto immunogeno.

Questo sistema diventa il più potente effettore della risposta immunitaria a livello delle mucose respiratorie.

IgA sieriche

Nel sangue le IgA interagiscono con un recettore Fc chiamato FcaRI, che è espresso sulle cellule effettrici immunitarie per avviare reazioni infiammatorie [20].

Il legame di FcaRI da parte di immunocomplessi contenenti IgA provoca citotossicità cellulo-mediata dipendente da anticorpi (ADCC), degranulazione di eosinofili e basofili, fagocitosi da parte di monociti, macrofagi e neutrofili e attivazione dell'attività di burst respiratorio da parte di leucociti polimorfonucleati [20].

IgA secretorie

L'elevata prevalenza di IgA nelle aree della mucosa è il risultato di una cooperazione tra plasmacellule che producono IgA polimeriche (pIgA) e cellule epiteliali della mucosa che esprimono il recettore delle immunoglobuline polimeriche (pIgR) [20].

Nell'intestino, le IgA possono legarsi allo strato di muco che ricopre le cellule epiteliali.

In questo modo si forma una barriera in grado di neutralizzare i patogeni prima che raggiungano le cellule epiteliali.

La produzione di IgAs contro antigeni specifici dipende dall'attivazione delle cellule M (isolate solo recentemente le cellule M sono una sottopopolazione del MALT: sono cellule altamente specializzate e costituiscono il 10% delle cellule mucosali dell'intestino situate nei tratti sovrastanti i noduli linfatici (Placche di Peyer localizzate nella sottomucosa) e delle cellule dendritiche sottostanti, dall'attivazione delle cellule T e dal cambio di classe delle cellule B nei follicoli linfoidi isolati dell'intestino tenue (GALT) [21].

Prodotte localmente dalle plasmacellule che sono distribuite nelle ghiandole secretorie e nella lamina propria dei tessuti intestinali e respiratori, le IgAs vengono selettivamente trasportate nelle secrezioni esterne [22].

Le IgA secretorie difendono la mucosa respiratoria esplicando queste funzioni:

- ridotta penetrazione di virus (azione citopatica e ciliostatica);
- ridotta adesione alla mucosa bronchiale dei batteri che colonizzano abitualmente le vie aeree;
- ridotta penetrazione per diapedesi nella sottomucosa bronchiale dove avviene il processo infettivo.

Il sistema Immune IgAs ha una potente memoria immunologica ed è stimolato ripetutamente dal rinnovato contatto con gli antigeni che portano a più alti livelli di produzione queste specifiche IgA [23].

La somministrazione orale di un immunostimolante può sfruttare la grande quantità di tessuto linfoide presente nel cavo orofaringeo (tonsille palatine), nell'albero bronchiale (BALT) e nell'intestino (GALT).

È stato dimostrato che popolazioni specifiche di cellule linfoidi della mucosa non solo migrano e successivamente si localizzano nel sito di origine, ma si spostano anche in altri siti della mucosa come dal tratto gastrointestinale al tratto respiratorio [24,25].

Questi percorsi migratori, indicati collettivamente come "sistema immunitario della mucosa comune", aumentano le opzioni per incrementare la risposta immune anche impiegando la via orale [24,25].

Il quadro generale dell'immunità mucosale come già accennato coinvolge le cellule NK e le cellule dendritiche che iniziano il processo.

Gli effetti farmacodinamici del Buccalin® sono stati dimostrati anche da diverse pubblicazioni.

Studi in vivo

In uno studio randomizzato controllato con placebo, un totale di 80 volontari sani hanno ricevuto placebo o Buccalin® alla dose standard per 3 o 5 giorni [26].

Il ciclo è stato ripetuto dopo un intervallo di 60 giorni.

Un quarto gruppo ha ricevuto anche una dose dieci volte superiore alla dose suggerita per 5 giorni.

I test ELISA hanno evidenziato una specifica stimolazione del sistema immunitario verso i ceppi inclusi nel trattamento standard di entrambi i gruppi, con risposte di tipo "booster" dopo la seconda somministrazione [26].

Questa risposta non è stata vista nei soggetti che avevano ricevuto il placebo.

Un aumento nella risposta immune non specifica dopo somministrazione orale per cinque giorni è stato visto anche in un altro gruppo di volontari sani [27].

Lo schema di somministrazione attualmente suggerito (1 compressa il primo giorno, 2 il secondo giorno e 4 il terzo giorno) è stato testato in 20 volontari sani verso il placebo assunto da altri 20 pazienti [28].

Il contenuto di anticorpi verso *H. influenzae* nella saliva (IgA, IgM e IgG) mostrava un aumento con un picco circa 60 giorni dopo la somministrazione.

L'aumento nella risposta anticorpale, tuttavia, sembrava più alto in quei soggetti che avevano un più basso livello di anticorpi al basale.

Lo stesso schema – 1 + 2 + 4 – in 10 volontari sani – ha prodotto un aumento dell'attività dei linfociti e dei PMN dai campioni di espettorato.

In circa il 40% dei soggetti si è visto un aumento degli anticorpi circolanti verso *S. aureus*, *S. Pneumoniae* e *S. haemolyticus* [29].

La somministrazione di una compressa di Buccalin® al giorno per sette giorni in pazienti femmine con età compresa tra 16 e 62 anni con broncopneumopatia cronica determinava un aumento nelle IgAs che andavano da 2,27 mg nelle prime 24 ore a 2,58 dopo 15 giorni e raggiungevano 5,20 mg dopo 25 giorni ($p<0,01$) [30].

Il livello di anticorpi circolanti (IgG, IgA e IgM) non mostrava nessun aumento a conferma che Buccalin® agisce come potente effettore dell'immunità mucosale.

Il trattamento con Buccalin® (una compressa il primo giorno, otto compresse dal secondo giorno e 16 comprese dal terzo giorno) in 20 pazienti con bronchite cronica ha determinato anche una significativa riduzione nella conta microbica dell'espettorato esaminato 20 giorni dopo il suo impiego [31].

La posologia 1 + 2 + 4, infine, era capace di aumentare l'attività fagocitica dei PMN nell'escreato di pazienti con bronchite cronica verso i controlli non trattati [32].

I livelli sia delle IgAs che delle IgA sieriche in 12 bambini (età da sei mesi a tre anni e mezzo) con frequenti infezioni respiratorie (cosiddetti "bambini catarrali") trattate con Buccalin®, al dosaggio di una compressa il primo e secondo giorno e due compresse al terzo giorno, hanno mostrato un incremento marcato.

Anche in questa popolazione, l'aumento è sembrato più alto nei pazienti con più basso livello al basale [33].

Un aumento significativo nelle IgAs e nell'indice di chemiotassi è stato visto anche in 16 bambini "catarrali" – età da 15 mesi a sei anni – trattati con tre cicli mensili di Buccalin® 1 + 1 + 2 verso otto pazienti di controllo [34].

Efficacia clinica

Buccalin® è presente sul mercato da molti anni, e le prime evidenze pubblicate risalgono al 1956.

I trial più rilevanti, pubblicati sull'uso di Buccalin®, insieme ai loro principali risultati, sono riassunti nella Tabella 1 seguente.

Popolazione generale

La prima somministrazione 1+ 2+ 4 (compresse) risale alla metà degli anni '50 [35].

In questo studio controllato, l'incidenza dell'influenza in 68 lavoratori austriaci non vaccinati con Buccalin® era del 29%, mentre in 172 lavoratori vaccinati era dell'11%. ($p<0,01$).

Un altro studio ha confrontato i giorni di assenza dal lavoro di 100 dipendenti di una società mineraria francese vaccinati con Buccalin® 1 + 2 + 4 e 100 controlli (soggetti non vaccinati) [36].

Il numero totale di giornate lavorative perse nel periodo considerato è stato di 84 nel gruppo di controllo e di 14 nel gruppo Buccalin®.

Ottimi risultati sono stati ottenuti in 582 lavoratori ai quali è stato somministrato Buccalin® per prevenire le complicanze influenzali.

Una significativa riduzione degli episodi di malattia e delle assenze dal lavoro è stata osservata nel gruppo arruolato rispetto a quelli degli anni precedenti alla vaccinazione.

Inoltre, è stata riscontrata una significativa diminuzione delle infezioni respiratorie acute nei soggetti a cui sono stati somministrati vaccino antinfluenzale e Buccalin® ed una riduzione delle assenze dal lavoro [37,38].

A questo riguardo uno studio retrospettivo con lo scopo di valutare l'incidenza di malattie respiratorie in 1.550 soggetti trattati con 1 + 2 + 4 Buccalin® e 1.415 soggetti non trattati (impiegati pubblici) riportavano i seguenti risultati [37]: nel gruppo trattato l'incidenza delle patologie respiratorie era 16,4% verso 29%; nel gruppo non trattato.

I giorni di assenza dal lavoro erano 750 per i soggetti trattati e 2.140 per i soggetti non trattati [37].

Si può affermare che i soggetti trattati con Buccalin® hanno presentato anche una sintomatologia meno grave

Tabella 1 Evidenza scientifica su Buccalin®. Dati raccolti e rielaborati da autori.

Autore	Anno	Paese	Design Studio	Popolazione	N. pazienti arruolati	N. pazienti trattati
Carlone	2014	Italia	Doppio cieco, placebo-controllato	Infezioni respiratorie	188	90
Clancy	1983	Australia	Doppio cieco	PD volontari sani	40	20
Cogo	2012	Italia	Retrospettivo	Anziani con BPCO	33	33
Clancy	1983	Australia	Doppio cieco	PD volontari sani	40	20
de Mattia	1978	Italia	Controllato	Bambini con infezioni respiratorie	21	12
de Ritis	1975	Italia	Aperto	Donne con patologie respiratorie	16	16
Fattorossi	1992	Italia	Studio "case-control"	Volontari sani	10	10
Guerra	1992	Italia	Randomizzato	Soggetti con anamnesi di broncopolmonite o infezioni ricorrenti respiratorie	90	60
Meidl	1956	Austria	Controllato	Popolazione generale non vaccinata	240	172
Melino	1970	Italia	Controllato	Popolazione generale non vaccinata	2.965	1.550
Melino	1975	Italia	Controllato	Popolazione generale vaccinata e non vaccinata	6.466	3.156
Melino	1975	Italia	Controllato	BPCO (associazione con vaccino antinfluenzale)	3.078	649
Ramponi	2015	Italia	Retrospettivo	Infezioni respiratorie nella popolazione pediatrica	70	70
Zanasi	1992	Italia	Randomizzato	BPCO	26	13
Wegmann	1972	Svizzera	Controllato	Popolazione generale non vaccinata	1.934	624
Mastroeni	1984	Italia	Aperto	BPCO	20	20
Maroto Blanco	1966	Spagna	Controllato	Soggetti non vaccinati	200	100
Cardani	1991	Italia	Controllato	Bambini con infezioni ricorrenti respiratorie (RRTI)	20	20
de Bernardi	1987	Italia	Controllato	BPCO (in associazione con vaccino antinfluenzale)	30	15
Oggiano	1985	Italia	Controllato	Bambini con infezioni respiratorie (ricorrenti RTIs)	24	16
Scotti	1987	Italia	Aperto	Infezioni ricorrenti respiratorie (RTIs)	36	22
TOTALE					**15.507**	**6.668**

rispetto al gruppo dei non trattati con un minor numero di giornate lavorative perse [37].

Un altro studio condotto in Svizzera ha mostrato un 30% di riduzione nel numero di episodi di raffreddore ed influenza (p<0,001) [39].

La posologia 1 + 2 + 4 (ripetuta ogni 30 /40 giorni) mostrava un beneficio aggiuntivo alla somministrazione del vaccino antinfluenzale.

Un altro grande studio, con lo scopo di valutare l'andamento dell'epidemiologia delle malattie respiratorie nel semestre "ottobre 1974-marzo 1975", ha esaminato 6.466 dipendenti di un ministero italiano che sono stati divisi in quattro gruppi [38]:

- gruppo di controllo (incidenza di episodi respiratori correlati all'infezione 23,5%);
- Buccalin® – tre cicli di terapia (5,4%);
- vaccino antinfluenzale (3,7%);
- Buccalin® (tre cicli di terapia) più vaccino antinfluenzale (1,9%).

La durata degli episodi era significativamente più bassa nella popolazione trattata.

Risultati positivi sono stati osservati anche sulla gravità dei sintomi e sulla risposta immune [38]:

- 19,2% dei soggetti non trattati;
- 4,3% dei soggetti che hanno assunto Buccalin®.

Analogamente uno studio osservazionale retrospettivo ha valutato l'incidenza di riacutizzazioni in una popolazione di broncopneumopatici cronici [38].

I principali risultati hanno riportato che l'incidenza di riacutizzazioni è stata dell'8,4% in 649 pazienti trattati con vaccino antinfluenzale + 3 cicli di Buccalin® (1 + 2 + 4) distanziati di circa un mese vs. una percentuale del 25% in 2.429 controlli non trattati [38].

Questi risultati sono stati confermati in uno studio successivo dove 30 pazienti con bronchite cronica erano stati randomizzati a ricevere placebo o Buccalin® 1 + 2 + 4 ripetuto ogni mese per 7 mesi più il vaccino antinfluenzale [40].

Il numero di riacutizzazioni era dimezzato nel gruppo vaccinato mentre nel gruppo di controllo i parametri di funzionalità respiratoria (FEV_1, ecc.) rimasero costanti o peggiorati [40].

Inoltre, una valutazione dell'efficacia del Buccalin® nella riduzione della durata degli episodi infettivi in una popolazione generale adulta è stata effettuata da Carlone e colleghi in uno studio multicentrico in doppio cieco controllato randomizzato prospettico verso placebo [41].

187 soggetti con una storia di precedenti episodi infettivi delle vie respiratorie sono stati randomizzati:

- a ricevere Buccalin® (4 cicli di trattamento con durata di 30 giorni);
- 93 hanno ricevuto placebo e sono stati monitorati per 6 mesi.

L'obiettivo primario dello studio era il confronto tra il Buccalin® e il placebo per verificare l'intervallo libero da sintomi da infezioni nei 6 mesi di follow up.

Gli endpoint secondari: numero di episodi e loro gravità.

I principali risultati mostravano che, durante il periodo di follow up dopo la fine del trattamento, il numero di giorni con infezione era 1,2 ± 4,3 nel gruppo placebo verso 0,5 ± 1,7 nel gruppo con Buccalin® (p=0,303) [41].

Inoltre, durante i sei mesi di follow up, il numero medio di giorni con sintomi da infezione (endpoint primario dello studio) era significativamente più grande (p=0,032) nel gruppo placebo (7,5 ± 10,6) rispetto al gruppo Buccalin® (6,6 ± 8,0)

Per quanto riguarda gli endpoint secondari dello studio, il numero totale di episodi infettivi non era significativamente diverso (p = 0,671) tra placebo (0,9 ± 1,2) e Buccalin® (1,1 ± 1,2) [41].

Alla luce dei dati sopra riportati, si può affermare che nei soggetti con anamnesi di infezione respiratoria, Buccalin® si è dimostrato più efficace del placebo nel ridurre i giorni liberi da sintomi da infezione caratterizzati anche da una minore severità [41].

Buccalin® è stato ben tollerato come il placebo.

Da tali studi si evince che Buccalin® ha la capacità di indurre l'incremento delle IgAs che rispecchia la fisiopatologia del MALT.

Inoltre, tale farmaco ha mostrato un effetto positivo non solo nella riduzione di costi diretti (impiego di antibiotici, visite mediche e ospedalizzazioni), ma anche una riduzione dei costi indiretti (perdita di giorni di scuola e lavorativi).

È stato riscontrato un ritorno positivo per ciò che concerne la durata del quadro clinico e l'incremento dell'intervallo libero da successivi episodi infettivi sia nel distretto delle vie aeree superiori che inferiori.

Dagli studi emerge che 2 o 3 cicli di Buccalin® possono migliorare questi endpoint.

Pazienti "a rischio"

In un trial a gruppi paralleli, 90 pazienti con una storia di broncopolmonite o infezioni respiratorie ricorrenti sono stati randomizzati in questo modo [42]:

- nessun trattamento;
- Buccalin® 1 + 2 + 4 ripetuto dopo tre mesi;
- Buccalin® più IgG per via parenterale.

Il numero totale di episodi infettivi nel gruppo di controllo è stato di 98 e 57 nel gruppo Buccalin®; 47 nel gruppo Buccalin® più IgG [42].

È interessante notare che un recente studio retrospettivo è stato condotto sulle cartelle cliniche di 68 pazienti (età media 71 anni) con BPCO in stadio GOLD II-IV [43].

Le frequenze delle riacutizzazioni infettive nell'anno di trattamento (2009 /2010) sono state registrate e confrontate con le frequenze negli stessi soggetti nell'anno precedente [43].

A questo proposito, i principali endpoint di efficacia valutati sono stati la riduzione di almeno un episodio infettivo durante l'anno di trattamento rispetto all'anno precedente.

I risultati hanno mostrato la capacità di Buccalin® di ridurre il numero degli episodi, durata, gravità e ospedalizzazioni [43].

Pazienti pediatrici

Un programma di somministrazione graduale (1 + 1 + 2 compresse) è stato testato nei bambini dai 6 mesi agli adolescenti ed è risultato sicuro ed efficace [33,44].

Buccalin® è stato testato con successo in bambini con ricorrenti infezioni respiratorie di età compresa tra 6 mesi e 15 anni dove ha mostrato un significativo miglioramento nei parametri dell'immunità umorale e nel numero degli episodi [33,44].

Un gruppo di 20 giovani pazienti con una storia di ricorrenti infezioni respiratorie (13 pazienti tra 5-10 anni; età media 10,9 anni) è stato trattato con Buccalin® 1 + 1 + 2 ogni mese per tre mesi.

Il dosaggio di IgAs è aumentato significativamente dopo ogni trattamento.

Il confronto con la stagione precedente in termini di numero di episodi infettivi ha evidenziato un netto miglioramento in 12 pazienti con un miglioramento "moderato" in 5 su 20 pazienti valutati [44].

Un aumento delle IgAs, della chemiotassi e una diminuzione del numero e della durata degli episodi infettivi rispetto a 8 controlli non trattati è stato osservato anche in 16 "bambini catarrali" di età compresa tra 15 mesi e 6 anni trattati con tre cicli mensili 1 + 1 + 2 di Buccalin®.

In un altro trial 14 bambini (età 1-6 anni) con almeno 6 episodi di infezioni respiratorie ricorrenti l'anno, sono stati trattati con tre cicli mensili di Buccalin® (posologia 1 + 1 + 2) [45].

In questi pazienti è stato riscontrato un notevole miglioramento nel numero di episodi, nella loro durata e nel numero di giorni di assenza da scuola, soprattutto quando paragonati a un gruppo di controllo di 14 bambini non trattati.

Inoltre, è stato condotto uno studio retrospettivo su 70 bambini (età media 9,2 anni) in due ambulatori del Nord Italia, trattati almeno con un ciclo di Buccalin® nel periodo 2008-2013 [46].

I principali risultati hanno mostrato una riduzione significativa nel numero degli episodi infettivi.

In aggiunta è stato riscontrato che l'efficacia veniva positivamente influenzata dal numero dei cicli di trattamento (1 ciclo verso 3 cicli).

Si può presumere, come riportato dagli autori, che la somministrazione di Buccalin® nei pazienti pediatrici può avere un effetto positivo sulla riduzione del numero di episodi ricorrenti correlati ad infezione respiratoria [46].

Le evidenze pubblicate, sia quelle originatesi negli anni 70/90, sia i dati sperimentali recenti, dimostrano che Buccalin® possiede un effetto immunostimolante positivo essenzialmente attraverso una maggiore produzione di IgAs.

La mancanza di studi più recenti è spiegata dal fatto che, dal 1970 in poi, il Buccalin® è stato considerato un "farmaco consolidato" con un chiaro insieme di indicazioni e con un buon profilo di tollerabilità.

La necessità di ulteriori studi, quindi, non è stata considerata.

La popolazione studiata è stata eterogenea ma tutte le indicazioni sono riconducibili alle proprietà di Buccalin® nella riduzione dell'incidenza di episodi infettivi minore intensità e durata degli stessi.

A questo riguardo anche considerando che gli studi risalgono a circa 30 anni fa, Buccalin® ha dimostrato una notevole efficacia sia nella popolazione pediatrica e adulta che in pazienti con fattori di rischio aggiuntivi rappresentati dalle comorbilità

Inoltre, alcuni studi hanno confermato il profilo favorevole di Buccalin® quando somministrato insieme al vaccino antinfluenzale mediante un'attività sinergica sulle infezioni spesso gravate sia da conseguenze cliniche che economiche.

In conclusione, in accordo alle evidenze pubblicate, Buccalin® non può essere considerato un reale vaccino ma un approccio complementare ai trattamenti convenzionali con lo scopo di ridurre l'incidenza di complicanze batteriche, coinfezioni e sovra infezioni che incidono in una percentuale non indifferente su pazienti con virosi respiratorie

METANALISI

Un sottoinsieme di 11 articoli dei 20 elencati nella Tabella 1 è stato selezionato anche per eseguire una metanalisi.

Gli articoli sono stati selezionati sulla base degli endpoint riferiti: numero, durata e gravità degli episodi infettivi respiratori nella popolazione trattata e nella popolazione di controllo.

La metanalisi è stata eseguita utilizzando il pacchetto "meta" (versione 6.2-1) in esecuzione con R 4.1.0 su un computer Windows 10 e applicando la funzione "MetaInc".

I risultati sono riassunti nel grafico a foresta (Forest Plot) (Figura 5).

Anche in presenza di un relativamente alto grado di eterogeneità (82%), probabilmente dovuto all'arco di tempo coperto e alla differente popolazione considerata (bambini adulti e pazienti anziani), il trattamento con Buccalin® ha mostrato un effetto statisticamente signi-

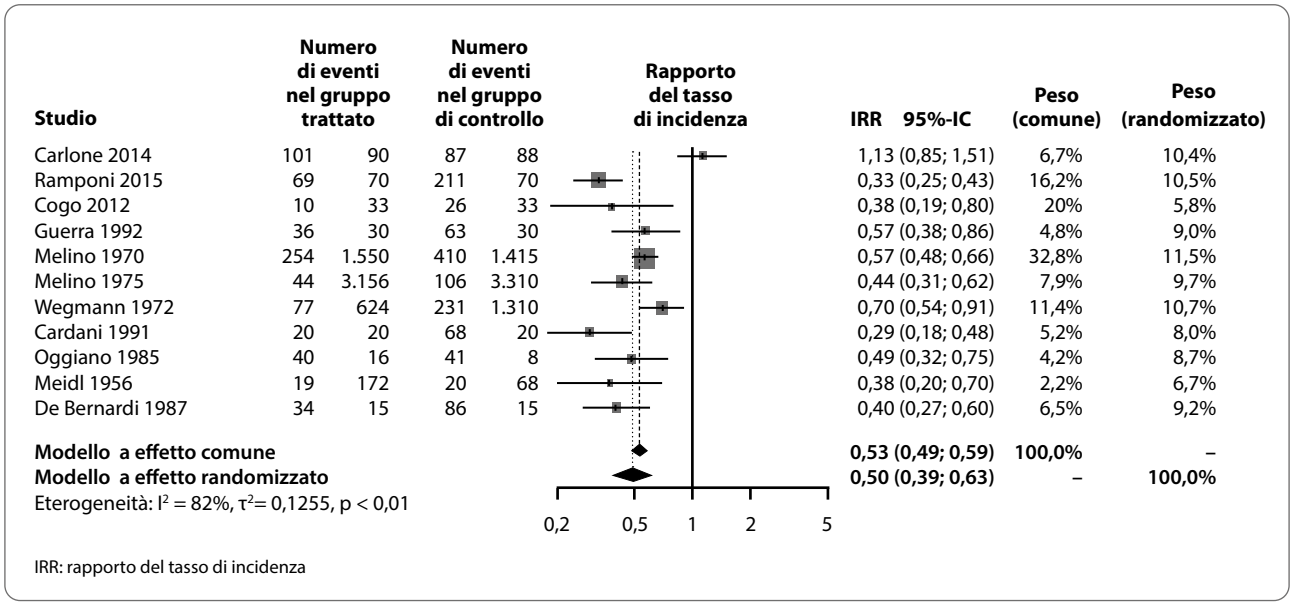

Figura 5 Grafico a foresta della metanalisi eseguita sugli studi clinici Buccalin (Funzione MetaInc della Library Meta, R 4.1.0).

ficativo sull'endpoint considerato negli studi analizzati: Incidence Risk Ratio (IRR) 0,53 (IC 0,49-0,59) e 0,50 (IC 0,39-0,63), sia per il modello a effetti comuni che per il modello a effetti casuali.

SICUREZZA

Dall'analisi della letteratura sui lavori pubblicati, che hanno interessato un totale di circa 15.000 pazienti (dei quali quasi 6.500 trattati con Buccalin®) il farmaco è sicuro e ben tollerato.

Negli studi di Cogo e colleghi, non è stato riportato alcun aumento delle reazioni avverse rispetto al placebo [43].

Carlone e autori hanno rilevato 17 eventi avversi nel gruppo trattato con il Buccalin® e 20 eventi avversi nel gruppo placebo [41].

La maggior parte degli eventi avversi sono stati da lievi a moderati (33/35, 94,3%) e si sono risolti durante lo studio (30/35, 85,7%) [41].

Gli effetti riportati sono stati mal di testa, dolore addominale, diarrea, costipazione, flatulenza e sintomi simil-influenzali.

3 eventi avversi, occorsi in un soggetto del gruppo placebo, sono stati considerati correlati al farmaco (malessere), anche 4 eventi avversi occorsi in 4 differenti soggetti del gruppo del trattamento attivo sono stati considerati farmaco correlati (diarrea, sindrome influenzale, allergie cutanee e bronchite) [41].

Tutti questi eventi avversi si sono risolti e soltanto in un caso (allergia cutanea) il trattamento ha richiesto l'uscita dallo studio [41].

Una recente pubblicazione su 70 pazienti pediatrici (Uso di un immunomodulatore batterico (Buccalin®) nella prevenzione delle infezioni respiratorie ricorrenti in pazienti pediatrici) conclude che nessuna reazione avversa è stata osservata al Buccalin® [46].

Va notato anche che "un sovradosaggio ripetuto" di Buccalin® non ha causato alcun aumento delle reazioni avverse rispetto al placebo.

DISCUSSIONE E CONCLUSIONI

Il Buccalin® è sul mercato da diverse decadi ed è stato usato da milioni di pazienti in diversi paesi.

Il Buccalin®, alla posologia raccomandata, ha dimostrato sicurezza ed efficacia sia nella popolazione pediatrica che adulta così come nella popolazione anziana e nei soggetti a rischio per patologie acute respiratorie ricorrenti.

I dati disponibili suggeriscono che l'effetto immunostimolante raggiunge il picco dopo 30 giorni dalla somministrazione e diminuisce lentamente in seguito: per questa ragione l'effetto ottimale si raggiunge ripetendo la somministrazione ogni 4-6 settimane in modo da garantire un'efficace immunomodulazione.

L'efficacia immunitaria dei vaccini orali non è stata pienamente chiarita.

Gli antigeni sono assorbiti a livello degli agglomerati linfoidi già noti come placche del Peyer's, presenti a livello intestinale.

Dopo essere stati processati da cellule presenti in tale distretto (cellule dendritiche e PMNs) attivano differenti linee cellulari (Linfociti T Helper, B, NK e T suppressor).

Questo consente la produzione di anticorpi specifici che lungo la via linfatica raggiungono le mucose respiratorie (Figura 6).

La mucosa respiratoria, con la presenza di questi anticorpi, diventa una barriera di difesa efficace verso la penetrazione degli agenti patogeni. In pochi casi si può verificare l'aumento degli anticorpi circolanti.

La somministrazione di Buccalin® è in grado di "ripristinare" la risposta immune.

In alcuni studi, infatti, l'effetto è stato visto essere più marcato nei soggetti con livelli più bassi al basale e meno evidente nei soggetti con valori vicini al normale.

Nei pazienti sottoposti al principio attivo sono stati visti sia un miglioramento nei parametri immunitari che una riduzione dell'incidenza e della durata degli episodi infettivi.

Gli effetti del Buccalin® sembrano essere anche sinergici con gli effetti della vaccinazione antinfluenzale.

In numerosi grandi studi sulla "popolazione generale" la somministrazione del principio attivo ha anche determinato una significativa riduzione nel numero e specie nella durata di episodi infettivi con una riduzione del numero di assenze dalle attività quotidiane.

Come precedentemente riportato il Buccalin® ha prima di tutto un robusto razionale farmacodinamico (basato sull'aumento delle IgAs dopo la somministrazione orale e dopo essere stato processato a livello intestinale) stabilito da articoli originali pubblicati sul tema e confermati da recenti dati clinici.

L'efficacia del prodotto è stata anche oggetto di numerose pubblicazioni nelle ultime 5 decadi e comprendente un totale di più di 15.000 pazienti.

L'indicazione autorizzata è stata infatti confermata da dati disponibili originati da studi sponsorizzati dal Marketing Authorization Holder (MAH).

Buccalin®, infatti, ha dimostrato la capacità di ridurre significativamente la durata degli episodi infettivi nella "popolazione generale" (in aggiunta ai trattamenti standard) e ha mostrato un effetto proporzionalmente più elevato nei bambini e nei pazienti anziani con BPCO.

La somministrazione di Buccalin®, infatti, non è curativa (l'efficacia in casi di patologie acute richiede un trattamento antinfiammatorio) e necessita di tempo (circa 2 mesi) per raggiungere il suo massimo effetto [28,41].

Il fatto che pazienti più compromessi (anziani e con patologie concomitanti e con un più alto numero di episodi) abbiano beneficiato in misura maggiore di questo trattamento rappresenta un ulteriore conferma della valenza di tale principio.

Inoltre, sia in pediatria che in patologie come la BPCO un numero più elevato di cicli sembra essere più efficace di una singola somministrazione.

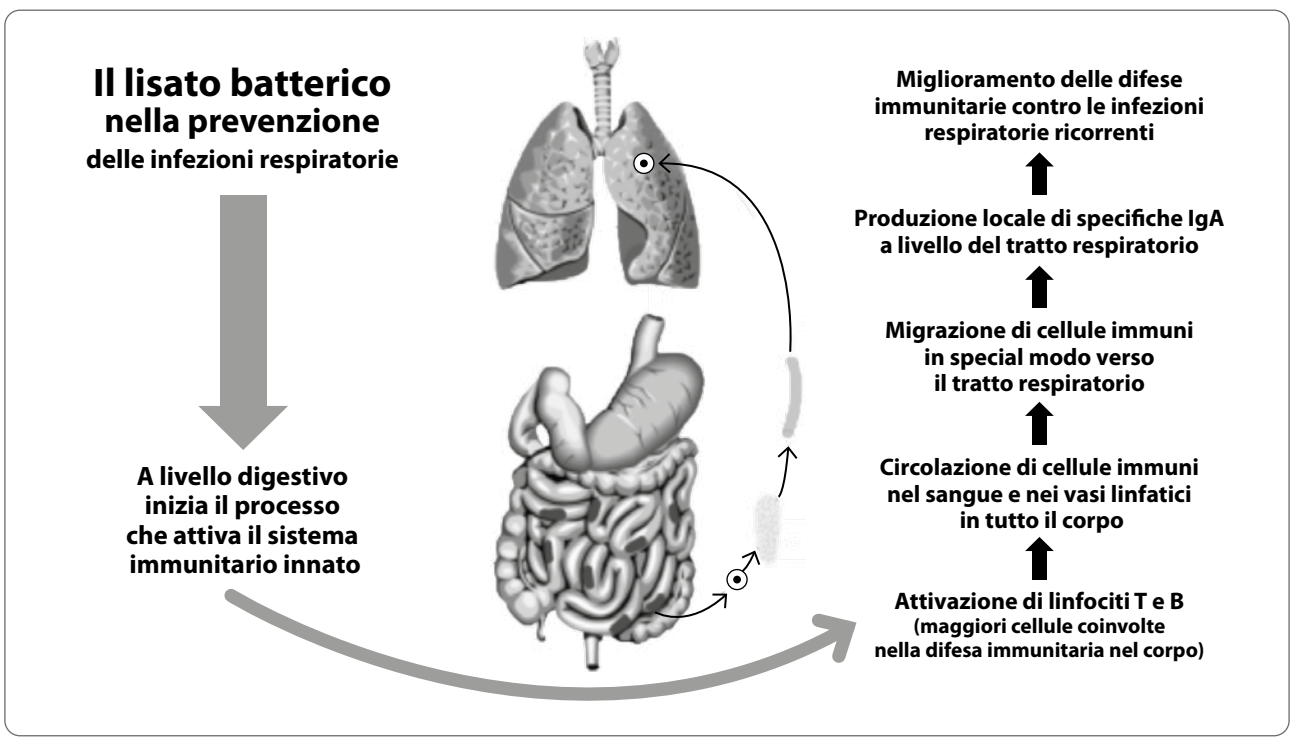

Figura 6 Il lisato batterico nella prevenzione delle infezioni respiratorie. Tratto da [47].

Le informazioni sul prodotto attualmente approvate potrebbero essere migliorate qualora si aggiungessero informazioni su alcune categorie di pazienti con infezioni ricorrenti, sia in pediatria che in età avanzata, per poter verificare gli esiti positivi a distanza di tale farmaco e per orientare meglio i medici a un razionale impiego del Buccalin®.

Per quanto riguarda la tollerabilità e reazioni avverse, secondo le evidenze pubblicate il farmaco ha dimostrato sicurezza e tollerabilità.

Anche con i limiti di una metanalisi retrospettiva su studi che coprono un lungo periodo di tempo e che interessano differenti popolazioni, i risultati ottenuti hanno evidenziato una riduzione statisticamente e clinicamente significativa della durata e gravità di eventi acuti respiratori confermando l'efficacia del Buccalin® nella popolazione generale, anche se incide in modo limitato sulla frequenza degli episodi.

Sotto il profilo farmaco economico si evince che Buccalin®, non solo ha ridotto i costi diretti correlati all'infezione (impiego di antibiotici), ma anche dei costi indiretti correlati alle varie attività (scolastica e lavorativa) e, in particolare modo, nei pazienti anziani all'assistenza domiciliare.

Conflitto di interessi

Gli autori dichiarano di non avere conflitti di interessi. GS è membro dell'Editorial Board di *Multidisciplinary Respiratory Medicine*.

Ricevuto: 5 luglio 2023
Accettato: 24 luglio 2023
Pubblicato: settembre 2023

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Comunicazione

a cura della Redazione

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Impact Factor di 2,3 per *Multidisciplinary Respiratory Medicine*

A fine giugno scorso Clarivate ha pubblicato la nuova edizione del Journal Citation Report relativo al 2022 e finalmente anche a *Multidisciplinary Respiratory Medicine* è stato attribuito un Impact Factor ufficiale pari a 2,3 punti. Le citazioni totali di MRM sulle altre principali riviste scientifiche mondiali incluse nel database del Journal Citation Report di Clarivate sono state 1.193. Nel ranking di competenza delle riviste del "sistema respiratorio" MRM è stata collocata in posizione 55/99.

Dopo anni di intenso impegno per raggiungere tale obiettivo l'Editor-in-Chief e la redazione intera non possono che essere soddisfatti e intendono esprimere la loro gratitudine a tutti coloro che nel tempo hanno contribuito allo sviluppo della rivista, *in primis* gli autori, i reviewers, i lettori e i membri del Board Editoriale. Nel contempo si è consci che il riconoscimento ottenuto è solo un punto di partenza per ulteriori progressi e uno stimolo a continuare a lavorare con serietà e metodo rispettando gli alti standard previsti nell'ambito delle pubblicazioni scientifiche accademiche internazionali.

Pertanto MRM, pubblicata in open access dal 2012 (https://mrmjournal.org/), continuerà a lavorare su queste basi per dare il suo contributo all'avanzamento della conoscenza e alla condivisione della ricerca scientifica.

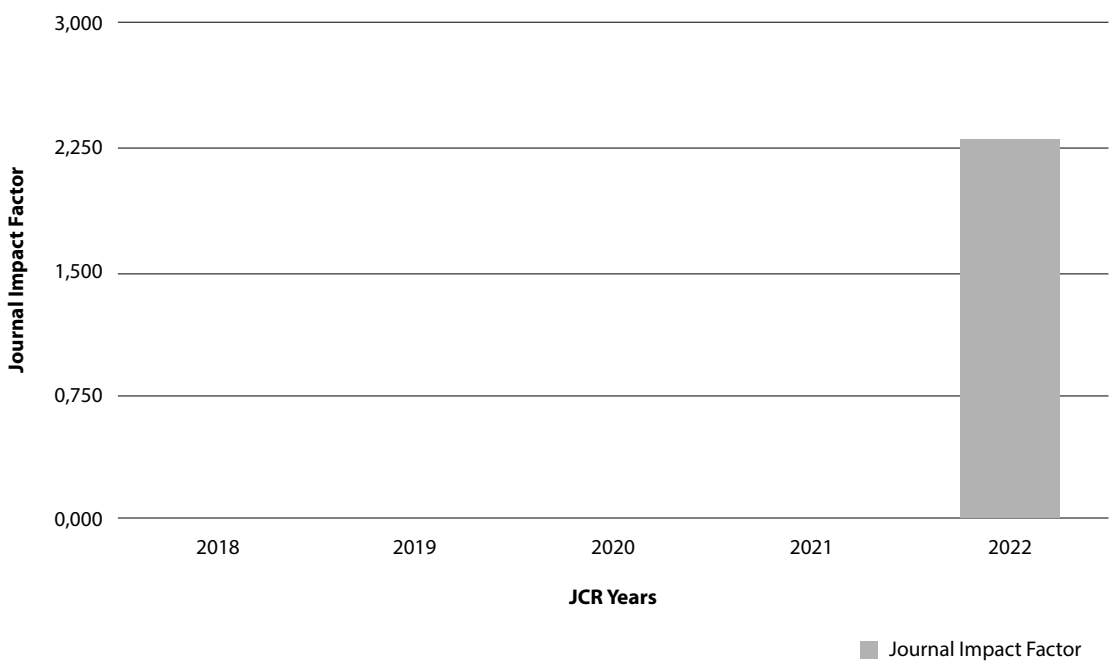

Figura 1 ***Multidisciplinary Respiratory Medicine*: 2022 Journal Performance Data.** (Fonte: Clarivate).

L'angolo della Cultura (non solo Medicina…)

a cura della Redazione

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Un dottore per il Ghirlandaio

Francesco Iodice
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email address: jodicef@tin.it

Venuta la sera, si mise a mensa con i Dodici.
Mentre mangiavano disse:
"In verità io vi dico, uno di voi mi tradirà".
Vangelo secondo Matteo, 26, 21"

La coppia, marito e moglie, vaga imbambolata attraverso una Firenze devastata dal terribile turismo "mordi e fuggi" e pervertita dall'insana globalizzazione. Mucchi selvaggi si aggirano dappertutto; i turisti - sandali e zainetto, panino e bibita in mano - sembrano ubiquitari; una buona parte sta ammassata davanti agli Uffizi o sul marciapiede della Galleria dell'Accademia, l'attesa media è di cinque ore. Nel "salotto" di via dei Tornabuoni di sera il disordine regna sovrano, imperversano i più svariati oggetti stesi su panni buttati quasi al centro della strada. Al cameriere (calabrese) del grande bar ad angolo con tavolini su piazza della Signoria viene rinnovata la richiesta del cocktail. Di sera, in una delle tante "buche" ristoratrici della città, non è possibile mangiare né la ribollita, e nemmeno la pappa al pomodoro o le pappardelle ai funghi porcini, ma solo novelle cuisine. Una città imbarbarita, che ha perso la sua identità, priva ormai di quell'atmosfera dove, fino ad alcuni anni fa, sembrava quasi di sentire le parole di padre Dante o di Macchiavelli. «*Non ti lamentare sempre*» dice lei conciliante, «*la città è diventata solo popolare; tutto qui. Parli come un intellettuale stagionato e classista con la puzza sotto al naso*». C'è il pretesto (questo sì classista!) secondo il quale sono solo i più acculturati e gli snob a giudicare pessimo ciò che lo è. È falso, non occorrono tre lauree o la lettura di Musil – ma solo due occhi e due orecchie – per capire che il concetto di "popolare" è una comoda menzogna per spacciare una cattiva cultura di massa con la scusa di "incontrare i gusti del pubblico". Timoroso di essere sopraffatto e distrutto dall'atmosfera barbarica, l'intellettuale stagionato scappa verso l'albergo: quella città diventata "furastiera" gli suscita, come in un'allucinazione, visioni di desertificazione, di giardini saccheggiati da nomadi e di palazzi in sfacelo nei quali pascolano greggi di pecore. Rivolge uno sguardo di rimprovero al portiere che gli ha consigliato la "buca" snaturata, sale in camera e medita la rivincita per l'indomani.

È una mattinata splendida, freddo secco e sole limpido: la coppia si avvia a passo deciso in posizione opposta alla moltitudine: tutti vanno a sinistra verso il centro e loro a destra, direzione borgo di Ognissanti. Nell'omonima piazza si affaccia la splendida facciata della chiesa in sobrio barocco fiorentino e affidata alla custodia di due soli frati; poco dopo, viene il portone del convento: attraversato il chiostro – dove il rumore dei passi offende un magico silenzio e dove un tempo i bambini si rincorrevano nei loro giochi e tiravano calci al pallone mentre i religiosi erano distratti (purtroppo, qualche pallonata si sarà pure stampata sugli affreschi di Jacopo Ligozzi e di Giovanni di San Giovanni, già segnati dai secoli e dall'incuria) – ecco il refettorio, famoso per il grande affresco dell'*Ultima Cena* del Ghirlandaio ("*fatto dalla*

Figura 1 La Chiesa di Ognissanti domina con una facciata nel sobrio stile barocco fiorentino l'omonima piazza a Firenze.

natura per fare il pittore") da non molto completamente restaurato, una celebrata opera del Quattrocento, più importante e più bella di quella che è nel museo del convento di San Marco. Nella sala vuota domina un'ombra silenziosa, finalmente un luogo solitario e un angolo di mondo senza voci. Per fortuna, la chiesa è esclusa dagli itinerari dei tour operator che mandano al massacro migliaia di loro clienti, indirizzandoli dall'altro lato della città dove Uffizi e Duomo tirano molto di più del capolavoro del Ghirlandaio.

Il Cenacolo, a dire il vero, sta lì per miracolo perchè era stato condannato a morte da due terribili nemici: l'alluvione del 4 novembre 1966 e la solfatazione. Il giorno dopo la terrificante marea di acqua e fango, appena le acque cominciarono a ritirarsi, sembrava che non ci fossero stati danni; dopo appena ventiquattr'ore il colore si staccò dal muro almeno dieci centimetri, sotto c'erano blocchi spessi di sale. Che fare? In quella drammatica emergenza i restauratori non avevano nulla, tranne un pacco di cotone idrofilo: presero dei batuffoli, li immersero nell'acqua e fecero cadere le gocce lentamente sui blocchi di sale, fin quando il sale si sciolse; come d'incanto il colore si riavvicinò alla parete e vi aderì, solo molto più tardi lo fissarono con sostanze speciali. Per quanto riguarda la solfatazione, essa si presentò con innumerevoli buchetti piccolissimi come punture di spillo, centinaia di migliaia se osservati al microscopio. Il colore era diventato polvere, bastava un soffio, un respiro e sarebbe caduto giù. Centinaia di migliaia di forellini quasi invisibili, che furono chiusi uno a uno con pennelli particolari; il danno maggiore era all'altezza dela tavola: una linea orizzontale e continua. Il "medico" che guarì l'affresco fu Giovanni Cabras, aiutato da Renato Castorini, un giovane collaboratore che stava con lui da oltre vent'anni. Hanno fatto praticamente un prodigio, bastava un colpo

Figura 2 Domenico Ghirlandaio, il Cenacolo di Ognissanti.

di spugna per distruggere tutto irreversibilmente, un'opera unica salvata senza strombazzamenti, come avviene in guerra in una trincea, quando un valoroso e sconosciuto medico strappa alla morte un soldato con un bisturi improvvisato.

Ora la coppia, seduta sulle apposite sedie trecentesche, si gode la scena con quegli apostoli e quel Cristo che sono di fronte a loro a pochi metri: la cena si svolge di giorno, nelle ore vicino al crepuscolo, quando Cristo, seduto al tavolo con i dodici apostoli, sta dicendo che uno di loro lo tradirà. Ghirlandaio guarda molto al Cenacolo di Andrea del Castagno in Sant'Apollonia: gli oggetti sulla tavola, i bicchieri, la trasparenza del vetro delle bottiglie. Un'ultima cena che sembra una rimpatriata fra vecchi amici senza la drammaticità di un destino che sta per compiersi; l'apostolo Giovanni ha la testa ciondoloni, forse ha bevuto troppo; Giuda, facile da riconoscere perché è seduto di spalle dall'altra parte del tavolo e tiene in mano una borsa col denaro avuto per il tradimento, ha lo sguardo di chi sta per tradire; bellissimo lo sfondo con i cipressi - che rappresentano la morte, le palme - che si riferiscono al martirio, gli aranci - che esprimono il Paradiso e il volo degli uccelli da preda che danno la caccia alle pernici, simbolo della vittoria del bene sul male. L'unico che non c'entra nulla è il Cristo, sembra assente e distaccato da ciò che accade intorno a lui, l'hanno rifatto nel XVII secolo; a dire il vero, è proprio bruttino. Ma la forza dell'opera d'arte rimane inalterata.

All'uscita tutti soddisfatti; l'"intellettuale" schizzinoso sentenzia: «*L'aver ammirato quest'affresco portentoso basta da solo a salvare la venuta a Firenze!*»; stavolta riceve il consenso anche della sua metà: «*Hai ragione, nei prossimi viaggi staremo attenti a prendere la direzione opposta a quella scelta dalla massa; e speriamo che ci vada sempre bene come oggi*». La gentildonna aveva concluso in un modo caro a La Palisse o a Catalano; in tutte le città avviene sempre la stessa cosa, due esempi su tutti: a Londra tutti visitano il British Museumo la National Gallery e ignorano la Wallace Collection o il Sir John Soane's Museum; a Napoli tutti si fanno traghettare a Capri o Ischia e nulla sanno del Pio Monte della Misericordia, dove troneggia la tela *Le Sette opere di Misericordia* del truce ma immenso Caravaggio o della chiesa di San Gregorio Armeno, la più bella chiesa barocca della città, nell'omonima via presepiale, dove nei quindici giorni che precedono il Natale orde "barbariche" si riversano a caccia di pastori o, peggio, dei personaggi del momento rappresentati dalla statuina. *Sic transit gloria mundi*.

Meeting Calendar

WHEN	WHERE	WHAT	WHO TO CONTACT
		2023	
September 9-13	Milan (Italy)	ERS International Congress 2023	www.ersnet.org
September 29-30	San Diego, CA (USA)	International CTEPH Conference	https://cteph2023.us/
October 2-4	Naples (Italy)	Skills course: "Paediatric bronchoscopy"	www.ersnet.org
October 5-8	Dubrovnik (Croatia)	2nd Niche-epithelial Stem Cell Interactions in Lung Health and Disease Conference	https://www.fusion-conferences.com/
October 8-11	Honolulu, Hawai (USA)	CHEST Annual Meeting 2023	https://www.chestnet.org/
October 9-11	Horn (Netherlands)	Course: "Pulmonary Rehabilitation"	www.ersnet.org
October 18-21	Marseille (France)	Skills course: Thoracoscopy and pleural techniques	www.ersnet.org
November 16-18	Wien (Austria)	Course: "Paediatric asthma"	www.ersnet.org
November 16-19	Singapore (EN)	APSR 2023: The 27th Congress of the Asian Pacific Society of Respirology	apsr2023.sg
November 23-25	Taormina, ME (Italy)	Congress: "Pneumomeeting 2023: I bisogni di aggiornamento in Medicina respiratoria"	www.pneumomeeting.it

Broncho Munal

ST 125-18
18.12.21

RIASSUNTO DELLE CARATTERISTICHE DEL PRODOTTO

1. DENOMINAZIONE DEL MEDICINALE

BRONCHO MUNAL Adulti 7 mg capsule rigide
BRONCHO MUNAL Bambini 3,5 mg capsule rigide
BRONCHO MUNAL Bambini 3,5 mg granulato in bustina

2. COMPOSIZIONE QUALITATIVA E QUANTITATIVA

BRONCHO MUNAL Adulti 7 mg capsule rigide
Una capsula rigida contiene:
OM-85 lisati batterici liofilizzati di Haemophilus influenzae, Streptococcus pneumoniae, Klebsiella pneumoniae ssp. pneumoniae e ssp. ozaenae, Staphylococcus aureus, Streptococcus pyogenes e sanguinis, Moraxella (Branhamella) catarrhalis
7,00 mg

BRONCHO MUNAL Bambini 3,5 mg capsule rigide
Una capsula rigida contiene:
OM-85 lisati batterici liofilizzati di Haemophilus influenzae, Streptococcus pneumoniae, Klebsiella pneumoniae ssp. pneumoniae e ssp. ozaenae, Staphylococcus aureus, Streptococcus pyogenes e sanguinis, Moraxella (Branhamella) catarrhalis
3,50 mg

BRONCHO MUNAL Bambini 3,5 mg granulato in bustina
Una bustina contiene:
OM-85 lisati batterici liofilizzati di Haemophilus influenzae, Streptococcus pneumoniae, Klebsiella pneumoniae ssp. pneumoniae e ssp. ozaenae, Staphylococcus aureus, Streptococcus pyogenes e sanguinis, Moraxella (Branhamella) catarrhalis
3,50 mg

Per l'elenco completo degli eccipienti, vedere paragrafo 6.1.

3. FORMA FARMACEUTICA

BRONCHO MUNAL Adulti 7 mg capsule rigide
Capsule rigide.
Capsule opache, con corpo e testa blu, contenenti una polvere da bianca a beige chiaro.
BRONCHO MUNAL Bambini 3,5 mg capsule rigide
Capsule rigide.
Capsule opache, con corpo bianco e testa blu, contenenti una polvere da bianca a beige chiaro.
BRONCHO MUNAL Bambini 3,5 mg granulato in bustina
Granulato in bustina.
Granulato beige chiaro.

4. INFORMAZIONI CLINICHE

4.1 Indicazioni terapeutiche

ADULTI:
Profilassi delle infezioni ricorrenti delle vie respiratorie (respiratory tract infections, RTI).

BAMBINI E ADOLESCENTI (età compresa tra 1 e 17 anni):
Profilassi delle infezioni ricorrenti delle vie aeree superiori (upper respiratory tract infections, URTI) nei bambini da 1 anno di età.

4.2 Posologia e modo di somministrazione

Posologia
ADULTI E ADOLESCENTI DI ETA' SUPERIORE AI 12 ANNI:
Il ciclo di trattamento profilattico per le infezioni ricorrenti delle vie respiratorie è:
Una capsula di BRONCHO MUNAL Adulti al giorno, da prendere a digiuno, per 10 giorni consecutivi al mese, per la durata di 3 mesi consecutivi.
Il ciclo di trattamento profilattico può essere ripetuto, se necessario.

BAMBINI FINO AI 12 ANNI DI ETA':
Stessa modalità di somministrazione degli adulti, poiché BRONCHO MUNAL Bambini contiene la metà della dose di BRONCHO MUNAL Adulti.

Modo di somministrazione
Uso orale.
Il contenuto della bustina va versato in una bevanda (acqua, succo di frutta, latte, ecc.) prima della somministrazione.
In pazienti che hanno difficoltà a deglutire la capsula, questa può essere aperta e il suo contenuto versato in una bevanda (acqua, succo di frutta, latte ecc.) prima della somministrazione, allo stesso modo della bustina.
La miscela si dissolve agitandola delicatamente. Si deve avvisare i pazienti di assumere tutta la miscela entro qualche minuto e di agitarla sempre appena prima di berla.

4.3 Controindicazioni
Ipersensibilità ai principi attivi o ad uno qualsiasi degli eccipienti elencati al paragrafo 6.1.
Bambini di età inferiore a 1 anno.
Malattie autoimmuni.
Infezioni intestinali acute.

4.4 Avvertenze speciali e precauzioni di impiego

Tracciabilità
Al fine di migliorare la tracciabilità dei medicinali biologici, il nome e il numero di lotto del medicinale somministrato devono essere chiaramente registrati.

Il trattamento deve essere sospeso in caso di febbre, in particolare all'inizio del trattamento.
Il paziente deve essere informato della possibilità, come evento indesiderato raro, di febbre elevata oltre i 39 °C, isolata e senza cause note, che deve essere differenziata dalla febbre che insorge a causa della patologia

originaria, sulla base delle condizioni laringee, nasali o otologiche; in caso di febbre elevata il trattamento deve essere sospeso e non ripreso.
Deve essere evitata l'assunzione concomitante di altri medicinali con attività immunomodulante aspecifica come quelli contenenti estratti batterici.
In alcuni casi è stata osservata l'insorgenza di attacchi d'asma in pazienti predisposti dopo l'assunzione di farmaci contenenti estratti batterici. In questo caso, BRONCHO MUNAL non deve essere assunto ulteriormente.
In caso di reazioni da ipersensibilità il trattamento deve essere interrotto immediatamente e non ripreso.
Non sono disponibili dati da studi clinici che dimostrano che l'uso di BRONCHO MUNAL possa prevenire la polmonite. Quindi la somministrazione di BRONCHO MUNAL per prevenire la polmonite non è raccomandata.

BRONCHO MUNAL non è indicato per il trattamento delle infezioni respiratorie acute ma esclusivamente per la prevenzione di recidive; non è tuttavia necessario sospendere la profilassi di recidive di infezioni respiratorie durante il trattamento di una infezione delle vie respiratorie in atto.

Eccipienti con effetti noti
Questo medicinale contiene meno di 1 mmol (23 mg) di sodio per capsula rigida / bustina, cioè essenzialmente 'senza sodio'.

4.5 Interazioni con altri medicinali ed altre forme di interazione

Non sono stati effettuati studi d'interazione con altri farmaci né con vaccini.
La risposta immunitaria può essere inibita nei soggetti con immunodeficienza congenita o acquisita, in terapia immunosoppressiva o con corticosteroidi.

4.6 Fertilità, gravidanza e allattamento
Gravidanza
I dati relativi all'uso di BRONCHO MUNAL in donne in gravidanza sono in numero limitato. Gli studi sugli animali non indicano effetti dannosi diretti o indiretti di tossicità riproduttiva.
A scopo precauzionale, è preferibile evitare l'uso di BRONCHO MUNAL durante la gravidanza.
Allattamento
Non essendo stati eseguiti studi specifici e non essendoci dati disponibili, come misura precauzionale è preferibile evitare l'uso del prodotto durante l'allattamento.
Fertilità
Gli studi sugli animali non mostrano effetti di BRONCHO MUNAL sull'indice di fertilità.

4.7 Effetti sulla capacità di guidare veicoli e sull`uso di macchinari
BRONCHO MUNAL non altera o altera in modo trascurabile la capacità di guidare veicoli e di usare macchinari.

4.8 Effetti indesiderati
Le reazioni avverse per BRONCHO MUNAL sono elencate in base alla classificazione MedDRA per sistemi e organi.
All'interno della classificazione per sistemi e organi, le reazioni avverse sono riportate in ordine di frequenza:

Molto comune:	≥1/10,
Comune:	≥1/100, <1/10,
Non comune:	≥1/1.000, <1/100,
Raro:	≥ 1/10.000, <1/1.000,
Molto raro:	<1/10.000,
Frequenza non nota:	non può essere definita sulla base dei dati disponibili.

MedDRA Classificazione Sistemica Organica / Frequenza	Reazione Avversa
Disturbi del sistema immunitario	
Non comune	reazioni di ipersensibilità (eruzione eritematosa, eruzione generalizzata, eritema, edema, edema palpebrale, edema del viso, edema periferico, gonfiore, gonfiore del viso, prurito, prurito generalizzato, dispnea)
Non nota	angioedema
Patologie del sistema nervoso	
Comune	cefalea
Patologie respiratorie, toraciche e mediastiniche	
Comune	tosse
Patologie gastrointestinali	
Comune	diarrea, dolore addominale
Non nota	vomito, nausea
Patologie della cute e del tessuto sottocutaneo	
Comune	eruzione cutanea
Non comune	orticaria
Patologie sistemiche e condizioni relative alla sede di somministrazione	
Non comune	affaticamento
Raro	piressia

In caso di disturbi gastrointestinali o disturbi respiratori di lunga durata, il trattamento deve essere interrotto.
In caso di reazioni cutanee, il trattamento deve essere interrotto poiché può trattarsi di reazioni allergiche.

Segnalazione delle reazioni avverse sospette
La segnalazione delle reazioni avverse sospette che si verificano dopo l'autorizzazione del medicinale è importante, in quanto permette un monitoraggio continuo del rapporto beneficio/rischio del medicinale. Agli operatori sanitari è richiesto di segnalare qualsiasi reazione avversa sospetta tramite il sistema nazionale di segnalazione al sito https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse.

4.9 Sovradosaggio

Non sono noti casi di sovradosaggio.

5. PROPRIETA' FARMACOLOGICHE

5.1 Proprietà farmacodinamiche
Categoria farmacoterapeutica: vaccino batterico; agente immunostimolante.
Codice ATC: J07AX.
Meccanismo d'azione
BRONCHO MUNAL ha mostrato proprietà immunomodulanti in vitro e in vivo nel corso di studi preclinici e clinici. Gli estratti batterici contenuti in BRONCHO MUNAL favoriscono una risposta antinfettiva aspecifica

(intensificazione della fagocitosi) mediata da risposte cellulari e umorali. E' stata osservata una risposta cellulare legata alla stimolazione dei linfociti B e T nonché l'induzione della produzione di citochine da parte di diversi tipi di leucociti e una risposta immunitaria umorale rappresentata dalla produzione di anticorpi di tipo IgA e IgG.

Effetti farmacodinamici

In alcuni studi, in seguito a trattamento con BRONCHO MUNAL, è stata osservata l'induzione di meccanismi di difesa immunitaria innati e/o adattativi; in dettaglio è stato osservato un aumento dell'IFN γ serico e del livello di immunoglobuline (IgA e IgG) circolanti.

In uno studio in aperto non controllato, condotto su 9 bambini affetti da deficit selettivo di IgA, è stato osservato un ripristino delle proprietà dei marcatori di membrana dei linfociti T e un aumento della risposta linfocitaria aspecifica.

In uno studio in doppio cieco, controllato con placebo, condotto sul lavaggio broncoalveolare di 20 soggetti affetti da bronchite cronica, è stato osservato un aumento dell'attività dei macrofagi alveolari (aumento della migrazione e della motilità, aumentato rilascio di O_2 in condizioni basali e dopo stimolazione).

Efficacia e sicurezza clinica

Adulti

In alcuni studi, in seguito all'associazione di BRONCHO MUNAL alla terapia di base, è stata osservata una minore frequenza di infezioni delle vie respiratorie (RTI) e di esacerbazioni della patologia di base in pazienti affetti da COPD/CB lieve o moderata, rinosinusite cronica o asma ricorrenti e di esacerbazioni delle infezioni in pazienti con condizioni respiratorie croniche di base, come COPD/CB lieve o moderata, rinosinusite cronica e asma.

In alcuni studi è stata osservata anche una riduzione del consumo di antibiotici o di altre terapie concomitanti.

Popolazione pediatrica

Il trattamento con BRONCHO MUNAL è stato associato ad una riduzione della frequenza di infezioni respiratorie acute in pazienti pediatrici con infezioni ricorrenti delle alte vie respiratorie o a rischio di URTI. In pazienti pediatrici con condizioni respiratorie croniche di base, il trattamento con BRONCHO MUNAL è stato associato ad una ridotta frequenza di esacerbazioni di rinosinusite cronica o tonsillite cronica e di manifestazioni respiratorie quali asma/sibilo.

In alcuni studi, il trattamento con BRONCHO MUNAL è stato associato ad una riduzione dell'utilizzo di trattamenti concomitanti, come antibiotici, antisettici locali o prodotti anti- infettivi, sedativi della tosse e mucolitici.

5.2 Proprietà farmacocinetiche

In base alla natura del prodotto, non può essere condotto uno studio farmacocinetico convenzionale, essenzialmente a causa della presenza di più componenti e dell'assenza di un metodo analitico idoneo.

Non ci sono dati disponibili relativamente ad assorbimento, distribuzione, biotrasformazione, eliminazione, linearità / non linearità, relazione(i) farmacocinetica(che) / farmacodinamica(che).

5.3 Dati preclinici di sicurezza

Tossicità a dose singola

La singola somministrazione endovenosa di OM-85 fino a 2,000 mg/kg nel topo e a 1,400 mg/kg nei ratti non ha provocato segni di tossicità.

Tossicità a dosi ripetute
La somministrazione orale ripetuta di OM-85 per 26 settimane nei ratti a dosi fino a 2,000 mg/kg/die e per 3 mesi nei cani a dosi fino a 100 mg/kg/die non ha rivelato effetti tossici.

Carcinogenicità
Non sono disponibili dati sulla possibile azione carcinogena di BRONCHO MUNAL dopo assunzione orale. L'esperienza clinica non fa supporre un effetto in tal senso.

Mutagenicità
I possibili effetti genotossici di OM-85 liofilizzato sono stati esaminati in una serie di saggi di tossicità genetica, costituiti da test di retromutazione batterica in vitro (test di Ames, che utilizza *S. typhimurium* ed *E. coli*), test dei micronuclei in vivo e test delle aberrazioni cromosomiche. OM-85 non ha indotto mutazioni nei saggi in vitro e in vivo.

Disturbi della fertilità
La somministrazione orale di OM-85 liofilizzato fino a una dose massima di 1.600 mg/kg/die a ratti maschi e femmine non ha mostrato alcun effetto sulla fertilità e sulla riproduzione. Il trattamento è stato ben tollerato e non ha influenzato le prestazioni di accoppiamento, i tassi di impianto e di aborto spontaneo, il numero di cuccioli per animale, il rapporto maschi/femmine e il peso del feto. Il comportamento riproduttivo e la fertilità della prima generazione erano normali e anche la prole della seconda generazione non ha mostrato anormalità.
In ratti femmina trattati durante la gestazione fino a 21 giorni dopo il parto con una dose massima di 1.600 mg/kg/die di OM-85, il comportamento, il parto e l'allattamento erano comparabili con quelli dei gruppi di controllo.

Teratogenicità
La somministrazione orale a ratti e conigli in gestazione fino a una dose massima di 1.600 mg/kg/die di OM-85 è stata ben tollerata e non ha causato effetti tossici significativi su embrioni o feti rispetto ai controlli.

6. INFORMAZIONI FARMACEUTICHE

6.1 Elenco degli eccipienti
Capsule rigide:
Amido di mais (pregelatinizzato), mannitolo, propile gallato anidro (E310), sodio glutammato anidro, magnesio stearato.
Composizione dell'opercolo della capsula: gelatina; titanio diossido (E171), indigotina (E132).
Granulato in bustina
Amido di mais pregelatinizzato, mannitolo, magnesio silicato, propile gallato anidro (E310), sodio glutammato anidro, magnesio stearato.

6.2 Incompatibilità
Non pertinente.

6.3 Periodo di validità
3 anni.

6.4 Precauzioni particolari per la conservazione
Questo medicinale non richiede alcuna condizione particolare di conservazione.

Conservare nella confezione originale per proteggere il medicinale dalla luce.

6.5 Natura e contenuto del contenitore
BRONCHO MUNAL Adulti 7 mg/Bambini 3,5 mg capsule rigide:
confezioni da 10 capsule rigide e 30 capsule rigide.
Le capsule sono confezionate in blister, con un lato di PVC/PVDC e l'altro di alluminio/PVDC.
BRONCHO MUNAL Bambini 3,5 mg granulato in bustina:
Confezione da 10 bustine.
Confezione da 30 bustine.
Bustine in accoppiato carta/alluminio/polietilene.
È possibile che non tutte le confezioni siano commercializzate.

6.6 Precauzioni particolari per lo smaltimento e la manipolazione
Nessuna istruzione particolare per lo smaltimento.
Il medicinale non utilizzato ed i rifiuti derivati da tale medicinale devono essere smaltiti in conformità alla normativa locale vigente.

7. TITOLARE DELL'AUTORIZZAZIONE ALL'IMMISSIONE IN COMMERCIO
ABIOGEN PHARMA S.p.A.
Via Meucci 36 – Ospedaletto - PISA

8. NUMERI DELL'AUTORIZZAZIONE ALL'IMMISSIONE IN COMMERCIO

BRONCHO MUNAL Adulti 7 mg capsule rigide - 30 capsule	A.I.C. n. 026609026
BRONCHO MUNAL Adulti 7 mg capsule rigide - 10 capsule	A.I.C. n. 026609014
BRONCHO MUNAL Bambini 3,5 mg capsule rigide - 30 capsule	A.I.C. n. 026609040
BRONCHO MUNAL Bambini 3,5 mg capsule rigide - 10 capsule	A.I.C. n. 026609038
BRONCHO MUNAL Bambini 3,5 mg granulato in bustina – 30 bustine	A.I.C. n. 026609053
BRONCHO MUNAL Bambini 3,5 mg granulato in bustina – 10 bustine	A.I.C. n. 026609065

9. DATA DELLA PRIMA AUTORIZZAZIONE/RINNOVO DELL'AUTORIZZAZIONE
Data del rinnovo più recente: Gennaio 2008

10. DATA DI REVISIONE DEL TESTO
Dicembre 2021

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E.C.M.

Il corso sarà inserito nella lista degli eventi definitivi ECM del programma formativo 2024 del Provider accreditato DYNAMICOM EDUCATION (cod. ID 181).

Chairmen

Francesco de Blasio
Mino Pelaia

LOCATION

Centro Congressi
HOTEL ARISTON
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Italy