Special Article

British Lung Foundation/United Kingdom Primary Immunodeficiency Network Consensus Statement on the Definition, Diagnosis, and Management of Granulomatous-Lymphocytic Interstitial Lung Disease in Common Variable Immunodeficiency Disorders

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A proportion of people living with common variable immunodeficiency disorders develop granulomatous-lymphocytic interstitial lung disease (GLILD). We aimed to develop a consensus statement on the definition, diagnosis, and management of GLILD. All UK specialist centers were contacted and relevant physicians were invited to take part in a 3-round online Delphi process. Responses were graded as Strongly Agree, Tend to Agree, Neither Agree nor Disagree, Tend to Disagree, and Strongly Disagree, scored +1, +0.5, 0, −0.5, and −1, respectively. Agreement was defined as greater than or equal to 80% consensus. Scores are reported as mean ± SD. There was 100% agreement (score, 0.92 ± 0.19) for the following definition: "GLILD is a distinct clinico-radio-pathological ILD occurring in patients with [common variable immunodeficiency disorders], associated with a lymphocytic infiltrate and/or granuloma in the lung, and in whom other conditions have been considered and where possible excluded." There was consensus that the workup of suspected GLILD requires chest computed tomography (CT) (0.98 ± 0.01), lung function tests (eg, gas transfer, 0.94 ± 0.17), bronchoscopy to exclude infection (0.63 ± 0.50), and lung biopsy (0.58 ± 0.40). There was no consensus on whether expectant management following optimization of immunoglobulin therapy was acceptable: 67% agreed, 25% disagreed, score 0.38 ± 0.59; 90% agreed that when treatment was required, first-line treatment should be with corticosteroids alone (score, 0.55 ± 0.51). **(J Allergy Clin Immunol Pract 2017;5:938-45)**

Key words: *Common variable immunodeficiency; Lung Disease; Interstitial; Complications*

INTRODUCTION

Although common variable immunodeficiency disorders (CVID) are primarily characterized by hypogammaglobulinemia and increased risk of infection, noninfectious autoinflammatory, autoimmune, and lymphoproliferative complications are also common.[1] Notably, 8% to 22% of people living with CVID develop an interstitial lung disease termed "granulomatous-lymphocytic interstitial lung disease" (GLILD), which is associated with reduced survival.[2] This important complication of GLILD has been little studied. Investigators have used different definitions, including diffuse radiological abnormalities and/or biopsy evidence of granulomatous inflammation, with lymphoproliferative changes including histologic patterns of lymphoid interstitial pneumonia (LIP), follicular bronchitis, and/or diffuse reactive lymphoid hyperplasia.[3] Impaired T-cell function leading to dysfunctional antigen handling has been proposed as a possible mechanism,[4] perhaps in association with reduced switched memory B cells,[5,6] and/or aberrant responses to viral infection.[7] Management is primarily based on small case series,[8-10] and there have been no controlled trials. This is unsatisfactory both for people living with GLILD and for health care professionals.

In 2015, a UK consortium from London (University College London, Barts and Imperial), Cambridge, and Oxford established a network of clinicians with an interest in GLILD, to develop patient literature, and to produce a consensus document on the definition, diagnosis, and management of GLILD in adults. This was funded by the British Lung Foundation and achieved in collaboration with the United Kingdom Primary Immunodeficiency Network, using Delphi methodology.

The Delphi technique, first used in the 1950s to assess the impact of new military technology, has been widely used in health care to develop consensus documents. Key characteristics include anonymity of the participants, structured flow of information, and faeedback to individuals of group data from previous rounds to inform subsequent responses.[11]

We report the results of a Delphi consensus process providing a statement on the definition, diagnosis, and management of GLILD in adults. This has not been previously performed and represents the largest report to date of collective clinical experience in GLILD. We provide a definition for future studies, illuminate current practice, and help to define future research priorities.

METHODS

A structured questionnaire containing a proposed definition of GLILD, and statements on diagnosis and management, was developed by the Steering Committee (Delphi Round 1).

For Delphi Round 2, all UK centers providing specialist immunology services were contacted via the UK Primary

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Immunodeficiency Network and asked to nominate interested consultant immunologists, chest physicians, radiologists, and pathologists to take part. The role of consultant in the United Kingdom signifies a senior physician who is on a national register in their respective specialty. Participants were therefore self-selected as those with an interest in GLILD. The number of participants was not restricted. These participants completed the questionnaire via a Web link (SurveyMonkey). Participants did not have to answer all the questions; thus, for example, a radiologist might only answer sections on radiology. We report the number of respondents for each question.

Responses were graded, unless stated otherwise, as Strongly Agree, Tend to Agree, Neither Agree nor Disagree, Tend to Disagree, and Strongly Disagree, scored +1, +0.5, 0, −0.5, and −1, respectively. This is illustrated as Figure 1. *A priori*, agreement was defined as 80% or greater consensus to Agree (Strongly or Tend to), or Disagree (Strongly or Tend to). Scores are reported as the mean and SD, on a scale of +1 to −1, with more extreme scores and lower SD indicating stronger consensus.

The Steering Committee reviewed the Round 2 summary responses and where further clarification was required, the question was adapted and sent back to participants with feedback from Round 2 as the third and final round. The process was designed to complete after the third round, reporting consensus or otherwise.

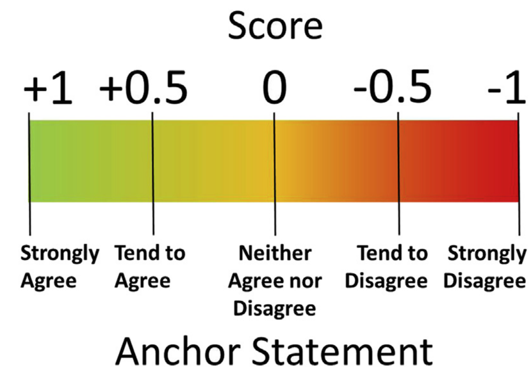

FIGURE 1. Anchor statements and scoring.

RESULTS

The Steering Committee that developed the questionnaire consisted of a facilitator (N.V., a senior trainee in Immunology) and 12 consultants: 5 immunologists, 4 chest physicians, 2 radiologists, and 1 pathologist.

Thirty-three consultants completed the second round Delphi, consisting of 17 immunologists, 8 chest physicians, 4 radiologists, and 4 pathologists. This included representation from 13 centers in total, including 6 of the 10 Royal College of Physicians "Quality in Primary Immunodeficiency Services (QPIDS)"-accredited centers. In total, the participating centers estimated that they currently cared for 112 patients with GLILD (median, 4; interquartile range, 5-9; minimum, 2; maximum, 24). Thirty-one consultants completed the third and final round Delphi.

Definition of GLILD

After revision for the final round Delphi, 24 of 29 strongly agreed and 5 of 29 tended to agree with the following definition of GLILD, which we therefore present as a British Lung Foundation/United Kingdom Primary Immunodeficiency Network consensus definition (100% agree; score, 0.91 ± 0.19): "GLILD is a distinct clinico-radio-pathological ILD occurring in patients with CVID, associated with a lymphocytic infiltrate and/or granuloma in the lung, and in whom other conditions have been considered and where possible excluded."

Importantly, there was also consensus that GLILD is usually seen in the context of multisystem granulomatous/inflammatory involvement that might include, for example, splenomegaly, lymphadenopathy, and/or liver disease, even if these manifestations are not symptomatic (93% agree; score, 0.66 ± 0.31).

Diagnosis of GLILD

There was no consensus that patients with GLILD must be symptomatic: 63% disagreed with this statement, score −0.27 ± 0.64. This was true for both major symptoms of GLILD: change in (or new) breathlessness (score, −0.22 ± 0.61) and change in (or new) cough (score, −0.29 ± 0.61); 96% agreed that the diagnosis of GLILD required a high index of suspicion, supporting a strategy of screening for respiratory complications of CVID.

A total of 88% agreed that the diagnosis of GLILD required discovery of new abnormalities on chest imaging (score, 0.65 ± 0.56) and therefore all respondents felt that a computed tomography (CT) scan was essential in the diagnostic workup (score, 0.98 ± 0.01). The results of consensus opinion on other aspects of the diagnostic workup are reported in Table I.

The other tests considered essential in diagnostic workup were full lung function (spirometry 96% agreed, 0.88 ± 0.27; lung volumes 91% agreed, 0.76 ± 0.40; and gas transfer 100% agreed, 0.94 ± 0.17), flexible bronchoscopy to exclude infection (83% agreed, 0.63 ± 0.50), and surgical lung biopsy (83% agreed, 0.58 ± 0.46); 96% preferred video-assisted thoracic surgical biopsy to open thoracotomy (score, 0.85 ± 0.28). There were no radiological findings considered sufficiently diagnostic to avoid the need for biopsy (score, −0.05 ± 0.61). There was no consensus that there had to be new change on lung function tests to make the diagnosis (54% agreed; 33% disagreed; score, 0.04 ± 0.67) and therefore the value of lung function testing is primarily in assessing progression and treatment response rather than establishing the diagnosis (as described further below).

There was no consensus on the need to perform other imaging tests (including chest x-ray and magnetic resonance imaging chest), functional tests (including oxygen saturation, 6-minute or shuttle-walk, or cardiopulmonary exercise testing), echocardiography, or blood tests (including inflammatory markers, β_2-microglobulin, serum angiotensin converting enzyme (ACE), or serum IgM). Despite GLILD usually being associated with multisystem involvement, there was no consensus for preference to biopsy another site in the presence of such manifestations even if that was more practical than surgical lung biopsy (score, 0.27 ± 0.59). This likely reflects the differential diagnosis in the lung discussed further below.

There was consensus that, where available, a diagnosis of GLILD should prompt a search for specific underlying genetic mutations, for example, LRBA/cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) (81% agree; score, 0.57 ± 0.36).

Radiology. Regarding the CT protocol, there was consensus that this should be thin slice (<2 mm, 80% agree; score, 0.73 ± 0.47) and contiguous (85% agree; score, 0.77 ± 0.38). There was no consensus about the administration of intravenous contrast (62% agree, 8% disagree; score, 0.40 ± 0.53).

TABLE I. Consensus on diagnostic workup of GLILD

Criteria	No. of respondents	% Agree	% Disagree	Mean ± SD score*
"The following tests are essential in the workup of suspected GLILD":				
Consensus				
CT Thorax	24	100	0	0.98 ± 0.01
Spirometry	24	96	0	0.88 ± 0.27
Lung volumes	23	91	4	0.76 ± 0.40
Gas transfer	24	100	0	0.94 ± 0.17
Flexible bronchoscopy to exclude infection	23	83	4	0.63 ± 0.50
Surgical lung biopsy	24	83	8	0.58 ± 0.46
No consensus				
Chest radiograph	23	65	9	0.48 ± 0.57
MRI Chest	21	0	48	−0.40 ± 0.46
Peripheral oxygen saturation	23	74	13	0.52 ± 0.65
6-minute or Shuttle-Walk Test	24	58	17	0.31 ± 0.57
Cardiopulmonary Exercise Test	23	0	57	−0.39 ± 0.40
Echocardiogram	24	33	29	0.06 ± 0.60
Serum CRP	23	52	26	0.15 ± 0.65
Serum β2-microglobulin	24	29	38	−0.06 ± 0.58
Serum ACE	24	50	25	0.25 ± 0.68
Serum IgM	24	29	25	0.04 ± 0.55
Percentage $CD21^{low}$ B cells	24	33	25	0.02 ± 0.40
Transbronchial biopsy	23	61	17	0.39 ± 0.62
Bronchoalveolar lavage cell differential	24	63	4	0.44 ± 0.52
Bronchoalveolar lavage immunophenotyping	23	30	17	0.00 ± 0.48

ACE, Angiotensin converting enzyme; *CRP*, C-reactive protein; *MRI*, magnetic resonance imaging.
*See text. Scale of −1 (strongly disagree) to +1 (strongly agree), with more extreme scores and smaller SD indicating greater consensus. Consensus defined as ≥80% agreement/disagreement.

Bronchoscopy. With regard to samples obtained at flexible bronchoscopy, the tests considered essential are reported in Table II. There was consensus to perform microscopy and bacterial culture (96% agreement; score, 0.93 ± 0.23), *Mycobacterial* culture (96% agreement; score, 0.93 ± 0.23), and fungal culture (91% agreement; score, 0.80 ± 0.33). There was no consensus for other tests at bronchoscopy including transbronchial biopsy, PCR for *Mycobacteria*, atypical pathogens, or viruses, routine tests for *Pneumocystis jirovecii*, or analysis of bronchoalveolar lavage fluid for cell differential or lymphocyte phenotyping.

Histopathology. There was 80% or more consensus (n = 20) that biopsy specimens should be immuno-stained for CD3, CD4, CD8, and CD20, for the presence of bacteria including *Mycobacteria* and fungi, and for clonality to exclude lymphoma. Two respondents additionally mentioned staining for viral markers including cytomegalovirus and EBV.

TABLE II. Consensus on diagnostic testing of bronchoalveolar lavage fluid obtained at flexible bronchoscopy for the investigation of suspected GLILD

Criteria	No. of respondents	% Agree	% Disagree	Mean ± SD score*
The following tests are essential in analysis of bronchoalveolar lavage from suspected GLILD:				
Consensus				
BAL Microscopy and culture	23	96	0	0.93 ± 0.23
BAL *Mycobacterial* culture	23	96	0	0.93 ± 0.23
BAL Fungal culture	23	91	0	0.80 ± 0.33
No consensus				
BAL PCR for *Mycobacteria*	23	61	9	0.46 ± 0.58
BAL PCR for atypical bacteria	23	70	9	0.50 ± 0.50
BAL PCR for respiratory viruses	23	74	4	0.61 ± 0.48
BAL PCR for *Pneumocystis jirovecii*	22	64	14	0.36 ± 0.56
BAL Silver stain or immunofluorescence for *P jirovecii*	21	48	10	0.31 ± 0.49

BAL, Bronchoalveolar lavage.
*See text. Scale of −1 (strongly disagree) to +1 (strongly agree), with more extreme scores and smaller SD indicating greater consensus. Consensus defined as ≥80% agreement/disagreement.

Differential diagnosis of GLILD

Respondents were asked to rate a list of radiological features as "necessary to make the diagnosis of GLILD," "typical of the diagnosis of GLILD," or "not typical of the diagnosis of GLILD." No features were consistently rated as necessary to make the diagnosis. More than 80% of (22 of 25) respondents rated the presence of solid nodules (*nodule* defined as <3 cm), semisolid nodules, pure ground-glass opacities, enlarged thoracic (hilar and/or mediastinal) lymph nodes, and splenomegaly as necessary or typical. More than 80% of respondents rated the presence of cysts and bronchiectasis as not typical. There was no consensus for reticulation, traction bronchiectasis, honeycombing, masses (defined as >3 cm), consolidation, or upper abdominal adenopathy. When nodules were present, there was no consensus about their distribution.

Results of the consensus on radiological differential diagnosis are presented in Table III. There was consensus that this includes infection, organizing pneumonia, lymphoid interstitial pneumonia, sarcoidosis, and lymphoma.

Respondents were also asked to rate a list of histopathological features as "necessary to make the diagnosis of GLILD," "typical of the diagnosis of GLILD," or "not typical of the diagnosis of GLILD." No features were consistently rated as necessary to make the diagnosis. More than 80% of the respondents rated the presence of granulomatous inflammation, peribronchiolar lymphoid proliferation, interstitial lymphoid proliferation, and CD4-cell predominance as typical. There was consensus that eosinophils were not typical. There was no consensus for the presence of organizing pneumonia, interstitial fibrosis, or paucity of B cells. Ninety-two percent agreed that the biopsy features are

TABLE III. Differential diagnosis of GLILD

Criteria	No. of respondents	% Agree	% Disagree	Mean ± SD score*
"The differential diagnosis of GLILD on radiology includes":				
Consensus				
Infection	25	96	4	0.72 ± 0.36
Organizing pneumonia	26	92	4	0.65 ± 0.37
Lymphoid interstitial pneumonia	26	81	12	0.52 ± 0.54
Sarcoidosis	26	88	12	0.62 ± 0.48
Lymphoma	26	96	0	0.69 ± 0.29
No consensus				
Nonspecific interstitial pneumonia	24	63	17	0.31 ± 0.55
Vasculitis	25	40	32	0.12 ± 0.55
Invasive mucinous adenocarcinoma	25	32	32	0.04 ± 0.54
Pulmonary metastases	25	28	64	−0.16 ± 0.55
"The differential diagnosis of GLILD on histopathology includes":				
Consensus				
Infection	26	94	6	0.81 ± 0.39
Organizing pneumonia	20	95	5	0.63 ± 0.43
Lymphoid interstitial pneumonia	20	80	5	0.70 ± 0.47
Sarcoidosis	22	95	5	0.75 ± 0.37
No consensus				
Nonspecific interstitial pneumonia	19	63	0	0.47 ± 0.42
Usual interstitial pneumonia	19	42	37	0.11 ± 0.70
Follicular bronchitis	18	72	6	0.53 ± 0.47
Hypersensitivity pneumonia	20	70	15	0.38 ± 0.56

*See text. Scale of −1 (strongly disagree) to +1 (strongly agree), with more extreme scores and smaller SD indicating greater consensus. Consensus defined as ≥80% agreement/disagreement.

sufficiently typical to make a confident diagnosis in a person known to have primary immunodeficiency.

Results of the consensus on histopathological differential diagnosis are also presented in Table III. There was consensus that this includes infection, organizing pneumonia, lymphoid interstitial pneumonia due to other causes/associations, and sarcoidosis.

Management of GLILD

There was strong support for decision making on management being led by a multidisciplinary team including immunologists, chest physicians, radiologists, and pathologists (n = 26, 100% agree; score, 0.90 ± 0.20), for patients to be managed in a multidisciplinary clinic comprising immunologists and chest physicians (n = 25, 96% agree; score, 0.90 ± 0.25), and for patients to have access to a nurse specialist (n = 25, 84% agree; score, 0.70 ± 0.43) and psychological support (n = 24, 96% agree; score, 0.79 ± 0.29) as necessary.

Ninety-one percent (n = 22; score, 0.68 ± 0.33) agreed that immunoglobulin therapy should be optimized to standard concentrations before initiation of specific therapy for GLILD, but there was no consensus about targeting a higher trough level (n = 22, 64% agreed, 9% disagreed; score, 0.39 ± 0.46).

There was no consensus about the routine use of antimicrobial prophylaxis in patients with GLILD (n = 21, 48% agreed, 19% disagreed; score, 0.21 ± 0.56). Where prophylactic antibiotics were given, the most commonly used agents were azithromycin and, particularly if there was a risk of *Pneumocystis*, cotrimoxazole. There was no consensus that macrolides should be the preferred agent because of potential anti-inflammatory activity.

There was no consensus about whether expectant management (monitoring without additional therapy) following optimization of immunoglobulin therapy was an acceptable strategy (n = 24, 67% agreed, 25% disagreed; score, 0.38 ± 0.59). We went on to explore, having made a diagnosis, which features of GLILD were associated with a decision to commence additional therapy, examining the presence or absence of symptoms, normal versus abnormal and stable versus deteriorating lung function. There was consensus to start treatment when patients were symptomatic with abnormal and deteriorating lung function (n = 17, complete agreement), asymptomatic with abnormal and deteriorating lung function (n = 17, 100% agree; score, 0.79 ± 0.25), and symptomatic with normal but deteriorating lung function (n = 16, 81% agree; score, 0.63 ± 0.53). There was consensus not to treat a patient who was asymptomatic with normal and stable lung function (n = 17, 94% agree; score, −0.79 ± 0.40). There was no consensus to treat or not for the remaining 4 options.

Ninety percent agreed that when specific treatment was required, first-line treatment for GLILD should be with corticosteroids alone (n = 21; score, 0.55 ± 0.51). Of these 21 respondents, all but 1 preferred oral prednisone (1 preferred intravenous methylprednisone). Of the 20 using oral prednisone, the minimum dose used was 10 to 20 mg/d, and the maximum 1 to 2 mg/kg/d. For a 70-kg subject, the median (interquartile range [IQR]) dose was 40 (30-70) mg/d. For respondents using prednisone with a second agent, the 2 most commonly used second agents were azathioprine (6 respondents) and mycophenolate (4 respondents).

The consensus results regarding second-line drug therapy are reported in Table IV. There was 80% or greater consensus for the following 3 drugs as second-line agents, with or without steroids, in decreasing order of support: azathioprine (n = 21, 100% agreed; score, 0.71 ± 0.25), rituximab (n = 21, 90% agreed; score, 0.67 ± 0.40), and mycophenolate (n = 21, 81% agreed; score, 0.62 ± 0.44). There was no consensus support for abatacept (though potential use in patients with specific genetic mutations was noted), anti-TNF agents, ciclosporin, hydroxychloroquine, methotrexate, sirolimus, or tacrolimus. There was no consensus that biopsy at a single time point could be used to guide future second-line therapy decisions: 43% agreed with the statement that second-line therapy could be guided by lung biopsy results and 24% disagreed with this (n = 21). The second-line agents that had been used in clinical practice, in alphabetical order, were as follows: abatacept, adalimumab, azathioprine, ciclosporin, hydroxychloroquine, infliximab, methotrexate, mycophenolate, and rituximab. Of the 22 participants responding to the question "Would you consider bone-marrow transplantation for GLILD?" 7 (32%) said yes, 7 said no, and 8 were unsure.

Regarding opportunistic infections in the context of immunosuppression for GLILD, 55% of respondents had seen

TABLE IV. Consensus on second-line drug therapy in GLILD

Criteria	No. of respondents	% Agree	% Disagree	Mean ± SD score*
Which of the following drugs would you consider as second-line therapy in GLILD?				
Consensus				
Azathioprine	21	100	0	0.71 ± 0.25
Rituximab	21	90	5	0.67 ± 0.40
Mycophenolate	21	81	5	0.62 ± 0.44
No consensus				
Abatacept	18	33	28	0.03 ± 0.50
Anti-TNF agents	17	29	47	−0.12 ± 0.57
Ciclosporin	16	25	25	0.00 ± 0.48
Hydroxyxchloroquine	19	42	32	0.07 ± 0.56
Methotrexate	17	35	29	0.03 ± 0.51
Sirolimus	18	28	28	0.03 ± 0.53
Tacrolimus	18	22	33	−0.08 ± 0.43

*See text. Scale of −1 (strongly disagree) to +1 (strongly agree), with more extreme scores and smaller SD indicating greater consensus. Consensus defined as ≥80% agreement/disagreement.

opportunistic infections including *Pneumocystis*, nontuberculous *Mycobacteria*, cytomegalovirus, varicella zoster virus, and 1 case of possible progressive multifocal leucoencephalopathy. Further research is required here because these data are not incidence rates.

There was consensus that treatment response (or progression) could be assessed using change in symptoms (n = 22, 91% agreed; score, 0.64 ± 0.38), change in lung function (n = 22, 91% agreed; score, 0.75 ± 0.40), and/or change in CT appearance (n = 22, 91% agreed; score, 0.77 ± 0.40). The single preferred test in 82% of 17 respondents was change in gas transfer (DL_{CO} and/or K_{CO}); 63% of 19 respondents considered a change in gas transfer of 10% to 20% to be significant and 21% considered a change of 20% to 30% to be significant. After initiation of therapy, response was first assessed a median (IQR) of 3 (1.5-3) months later in 22 respondents; 9% of 22 participants would not repeat a CT, but in those who would the median (IQR) time to repeat was 5.5 (5.5-7.5) months.

There was no consensus about preferred maintenance therapy, or indeed the need for maintenance thereapy, in clinically stable disease. In 24 respondents, 46% would prefer a second-line (noncorticosteroid) agent alone, 21% preferred a second-line agent with a minimum continuing dose of corticosteroid, 13% preferred corticosteroid alone, and 13% preferred to withdraw all therapy and monitor.

In clinically stable disease, 55% of 22 respondents monitored patients every 3 to 4 months, and 32% every 5 to 6 months; 55% of 22 respondents would consider a repeat lung biopsy in the event of relapse.

DISCUSSION

We present the first consensus statement on the definition, diagnosis, and management of adult GLILD. This is not an evidence-based treatment guideline, but it does permit individual centers to compare their management against consensus. We hope that the statements made below will be supported or challenged by future research in this neglected condition. The consensus is derived from 33 consultants working across 13 centers currently providing care to more than 100 patients with GLILD, with contributions from immunology, respiratory medicine, radiology, and pathology. It is therefore the largest record of shared experience in managing GLILD reported to date.

We propose that GLILD should be defined as "a distinct clinico-radio-pathological ILD occurring in patients with CVID, associated with a lymphocytic infiltrate and/or granuloma in the lung, and in whom other conditions have been considered and where possible excluded." There was consensus that GLILD is usually seen in the context of multisystem granulomatous and/or inflammatory disease.[6] Only by agreeing a definition can the field move forward with rational experimental studies. Operationally, this implies that a confirmed diagnosis of GLILD requires both pertinent CT and histopathological abnormalities. The diagnosis may be suspected, but not confirmed, when the CT changes are considered typical but no biopsy has been performed.

Patients with GLILD may or may not be symptomatic. Only abnormalities on chest CT scan were felt essential for the diagnosis, with chest x-ray insufficiently sensitive. Our results support the need to screen patients with CVID for lung complications. The workup of suspected GLILD requires contiguous thin-slice CT chest, full lung function tests (for subsequent monitoring), flexible bronchoscopy to exclude infection, and surgical lung biopsy (video-assisted thoracic surgical biopsy) to confirm the diagnosis and exclude differential diagnoses. There was no consensus around the use of bronchoalveolar lavage lymphocyte phenotyping, reflecting ongoing controversy in the literature,[12,13] nor around the use of transbronchial biopsy for which yield has been reported to be variable[14] or endoscopic bronchial ultrasound for lymph node sampling. Further studies are required to establish the feasibility of less invasive diagnostic strategies.

The radiological and histopathological differential diagnosis includes infection, organizing pneumonia, LIP due to other causes/associations, and sarcoidosis. Lymphoma is an additional radiological differential. These results are consistent with previous reports of the radiological features observed in GLILD,[15] and a recent report describing the heterogeneity of histopathological findings in GLILD.[16] However, there was consensus that biopsy features were sufficiently typical to make a confident diagnosis in a person known to have primary immunodeficiency. We defined consensus that lung biopsy specimens should be stained for CD3, CD4, CD8, and CD20, for the presence of bacteria including *Mycobacteria* and for fungi, and for clonality to exclude lymphoma. The differential diagnosis of LIP and sarcoid emphasizes the importance of assessing serum immunoglobulins in patients presenting with these conditions, to exclude primary immunodeficiency. In contrast to GLILD, sarcoid is typically associated with hypergammaglobulinemia, hilar adenopathy, and specific (upper zone predominant) distribution of nodules within the lung. Further work is required to confirm whether differences in bronchoalveolar lavage lymphocyte subsets are able to differentiate sarcoid from GLILD.[12,13] The diagnostic workup of granulomatous lung disease outside the context of known CVID would include a full occupational and exposure history, imaging, and autoimmune screen.

Immunoglobulin replacement should be optimized to standard guidelines before the initiation of therapy for GLILD. A major current limitation is the absence of information on the natural history of GLILD, but it has been reported that the disease may progress despite optimal immunoglobulin replacement,[17] which provides a rationale for active therapy. Ongoing observational studies such as Study of Interstitial Lung Disease in Primary Antibody Deficiency (STILPAD) will inform further on this. We were not able to reach consensus on whether initial expectant management was an acceptable treatment option, which therefore remains an open research question of particular relevance for asymptomatic patients. There was consensus to treat patients irrespective of symptoms in the presence of abnormal and deteriorating lung function (as described further below, and of the order of a 20% reduction in gas transfer), and also to commence treatment in those who were symptomatic with normal but deteriorating lung function. Further work is required on biomarkers of disease progression, for example, IgM and/or thrombocytopaenia.[18] We recognize that in current clinical practice, and the absence of screening for GLILD in CVID, many patients may have been managed "expectantly" because their lung disease has not (yet) been recognized.

There was consensus that when specific treatment for GLILD was recommended, initial treatment should be with oral corticosteroids alone, despite a restricted evidence basis for such practice. Steroids have been used in GLILD for many years.[9,14] The median (IQR) dose of prednisone equivalent deemed appropriate for a 70-kg subject was 40 (30-70) mg/d. Preferred second-line agents, alone or in combination with corticosteroids, were azathioprine, rituximab, and mycophenolate. Published case series are available to support the use of combination azathioprine and rituximab[8] and mycophenolate.[19] There was no consensus for other therapeutic approaches, including bone-marrow transplantation, and interventions for which case reports or case series do exist including ciclosporin,[20] anti-TNF therapy,[21,22] and abatacept (in the context of LRBA/CTLA-4 deficiency[10]). However, no prospective randomized trials have been undertaken to date, and the largest case series of second-line therapy describes only 7 patients.[8] Our results suggest that many other therapies had been tried, without published evidence of success or otherwise. It is important that as a community we report the results of trials of novel agents, whether or not they are associated with therapeutic success. Immunosuppression appears to be associated with an increased risk of opportunistic as well as conventional infections in this already immunodeficient cohort but there was no consensus on the routine use of antimicrobial prophylaxis. There was also no consensus on the approach to management of disease that is clinically stable, with some clinicians preferring to continue treatment and others to withdraw, with continued treatment consisting of corticosteroids and/or second-line agents. We recognize that treatment needs to be individualized, including taking account of comorbidities, and that treatment of other manifestations of immune-mediated and inflammatory complications of CVID may complicate the treatment of GLILD.

Treatment response or progression should be assessed using change in symptoms, lung function, and imaging. There are no currently accepted scores to measure symptoms (if present) in GLILD, although validated scores exist for both breathlessness (such as the Medical Research Council scale) and cough (such as the Leicester Cough Questionnaire). We suggest the need for a validated patient-reported outcome measure in GLILD. Although there was most support for imaging as the optimal modality to detect treatment response or progression, a reluctance to perform repeat CT scanning meant that the preferred test to assess progression and/or response to therapy was gas transfer. A change in gas transfer of the order of 20% was generally considered significant, assessed not more than 3 months after starting therapy. It is important to note that a "normal" lung function measurement does not exclude significant deterioration if a patient previously had supranormal physiology. What little data have been published would suggest that vital capacity in GLILD remains stable over time.[6] CT, if repeated, was generally performed after 4 to 6 months of therapy. It was noted that chest x-ray may be used to monitor disease, if changes are initially visible. Monitoring in stable disease was typically every 3 to 6 months.

Reflecting the complexity of management decisions, and the uncertainty inherent in treatment and monitoring, there was strong support for management decisions being made in a multidisciplinary meeting and clinic, with access to specialist nursing and psychological support as necessary. Uncertainty in management also mandates the need for further research. This Delphi process has been necessary because of the current absence of robust evidence on which to base clinical decisions in GLILD. We included an additional question on research priorities in our survey. The 2 most frequent responses were a trial of expectant versus immediate management and, for immediate management, a randomized trial of corticosteroid versus combination therapy, or a second-line agent alone, most frequently rituximab.

There are strengths and weaknesses of the Delphi method. Key strengths include participant anonymity, and the opportunity to revise opinions in the light of group results. Delphi is well suited to the development of consensus documents.[11] Potential disadvantages include low response rates, the time taken to complete the questionnaires (typically 20 minutes for Round 2 in this case), and the risk that the way feedback is presented can lead to convergence. Our participants were a large group of self-selected experts involved in the management of GLILD, including consultant immunologists, chest physicians, radiologists, and pathologists. All UK centers managing GLILD were invited to take part. However, individual experience remains limited, even in larger centers, and the process reports an average of such limited experience with the potential for convergence of opinion. It must also be recognized that the definition of consensus used, although defined *a priori*, is arbitrary,[23] and this is why we have elected to present the actual scores with SD in this report. Our definition of consensus at 80% or greater is above, and therefore more robust than the 75% median reported in a systematic review.[23]

GLILD is not new, with the first report of LIP in the context of hypogammaglobulinemia dating back to 1973.[24] However, although previously neglected, there is now increasing interest. We recognize it is likely that ongoing genetic studies will dissect the heterogeneity of CVID, and may provide the basis for a future "precision medicine" approach to treat the complications of CVID, including interstitial lung disease. Already this is reaching the clinic; for example, GLILD in the context of CTLA4 deficiency[25,26] being treated with abatacept.[10] The future may therefore see a move away from the term GLILD, and it is already recognized that a subset of patients with CVID are more likely to experience lung complications: those with late-onset combined immunodeficiency.[27] However, the time frame and feasibility of novel approaches remain undefined, and there is a current clinical imperative to establish the optimal treatment for GLILD for the benefit of our patients. As noted above, important observational cohort studies in GLILD, notably

STILPAD, are currently in progress and these will also inform future treatment and management strategies. Finally, it is possible that a deeper understanding of the pathogenesis of autoimmune/autoinflammatory pathology in GLILD may inform on the pathogenic mechanisms of other interstitial lung diseases. Meanwhile, we present this consensus statement to the community to promote debate. Most importantly, we aim to facilitate and support further research. Only by doing this can we move from this initial iteration of a consensus document to evidence-based treatment guidelines for people living with this neglected and challenging condition.

CONCLUSIONS

We present a consensus statement on the definition, diagnostic criteria, treatment, and monitoring of GLILD in CVID, which can serve as a rational basis for experimental studies. This is the largest collection of shared clinical experience in GLILD ever recorded.

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