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Bronchoscopic performance of bronchoalveolar lavage in germany – a call for standardization

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Abstract. Background: Bronchoalveolar lavage (BAL) is a widely used clinical tool in diagnosing interstitial lung diseases. Although there are recommendations and guidelines, the procedure is not completely standardized. Varying approaches likely influence the conclusiveness of BAL data and may be one reason for the divergent judgement of their value between different centers. **Objectives:** To evaluate how BAL is performed in Germany using an electronically based survey. **Methods:** We conducted a cross-sectional online survey among all members of the German Respiratory Society. **Results:** 608 members responded to the survey and of these 500 perform lavages. Most bronchoscopists (344/500) do not use a tube and have no anesthesiologist present during the procedure (405/500). Propofol is used by 76.8% and midazolam by 67.9% (n = 405), often in combination. A major difference was noted regarding the total volume of instillation. Many respondents use a predefined fixed amount of instilled volume (202/500), whereas an almost equal number use variable volumes based on the recovery (196/500). The minimum recovery volume predefined by 217/499 ranged from 3-150 ml (median 30 ml; mean 42.2 ± 55.1 ml). Most respondents did not transport their samples in special medium (61.5%) or on ice (72.8%). The average time between recovery and arrival at the lab was 115.6±267.0 min (n = 323). **Conclusion:** This study shows the broad spectrum of variations in the performance of BAL in Germany, which could have a negative effect on the method's clinical value. There is a need for training and standardization of BAL performance.

Key words: Bronchoscopy; bronchoalveolar lavage; interstitial lung disease; BAL survey

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Introduction

Bronchoalveolar lavages (BAL) were first performed in animal studies in 1961, aiming to harvest alveolar macrophages for research purposes (1,2). Three years later, this method was introduced in

humans (2,3). Apart from the diagnosis of infectious diseases, BAL is an important tool in the diagnosis of interstitial lung diseases (ILD)(4–6). However, its use for the diagnosis of ILD has varied over the decades. According to the ATS/ERS/JRS/ALAT statement on idiopathic pulmonary fibrosis (IPF) from 2011, BAL should not be performed for diagnostic evaluation of IPF in the majority of patients (7). This point of view changed, and now the current guideline on the diagnosis of IPF from 2018 recommends BAL again in the diagnostic algorithm of IPF (8). However, although a recommendation for BAL was made, there were strong and divergent opinions on the use of BAL in ILD within the guideline committee. Given the fact that members of this committee should mainly base their recommendation on published data, this heterogeneity is surprising and may be the result of different personal experience on the value of BAL. Although there are guidelines on the BAL procedure, the authors discovered that there is a huge divergence in the performance of the BAL procedure itself. It is likely that different approaches affect the results of BAL and, thus, influence and limit their clinical value. Such differences in real world experience may be one reason for the divergent judgement of the value of BAL between different centers. Therefore, we performed an electronically based survey, which evaluated the performance of BAL in Germany.

Materials and Methods

We conducted a cross-sectional survey (see supplementary material) among all members of the German Respiratory Society (DGP). Members were contacted by email. Their participation was voluntary and all collected data was pseudonymized. Members were sent a corresponding link. Using this link, participants answered questions online via a database that was specifically developed for this purpose. The survey questions were developed jointly by the authors and are shown in the Supplement. Since the methods could vary within a single medical institution, the questions applied to the specific survey participant and not to the method practiced at the institution. Members of the DGP who did not participate in the survey within 2 weeks were asked in a second email to take part. Members, who responded to the survey and do not perform BAL, stopped the survey after the first question.

All responses were evaluated in a pseudonymized form. The authors did not know which response corresponded to which survey participant. The present study is a survey of a bronchoscopy method (how do I perform a BAL). It was on a generalized technique on an individual physician level and not a patient-based data survey. Individual patient information or patient data were not collected. Thus, an ethics committee vote or patient consent was not necessary.

A descriptive data evaluation was performed by calculating absolute numbers, percentages, medians, and means. Whenever possible standard deviations are given. However in most cases the data are nominal and not continuous. In these cases median or absolute numbers were calculated. The participants entered the data directly into an electronic database. The data were transferred to an Excel file and finally imported into and calculated using JMP® 14.20, SAS Institute Inc.

Results

3070 members of the German Respiratory Society (DGP) were contacted to take part in the study. The survey was taken by 608 members, of these 500 performed BAL. BAL was done mainly for suspected sarcoidosis or ILD (63%; 315/500) followed by infections (22%; 110/500). The average number of BALs performed per year by the physicians who specified this was 162 ± 251 (95% CI: 139-185; n = 464).The primary outcome was transplant-free survival. Data was obtained from the Social Security death index and the electronic medical record. Date of last follow-up, death, or lung transplantation was recorded.

Technical requirements for BALs - flexible tube, rigid bronchoscope, or without tube

The vast majority of the bronchoscopists performed BAL without intubation (Figure 1). Only 79/500 (15.8%) respondents, routinely intubated with a flexible tube. Thirty bronchoscopists (6.0%) used a rigid bronchoscope for intubation. Since only 47 participants (9.4%) said that an anesthesiologist is present when performing the BAL, it can be concluded that the majority perform the procedure via a flexible tube without the support of an anesthesiologist.

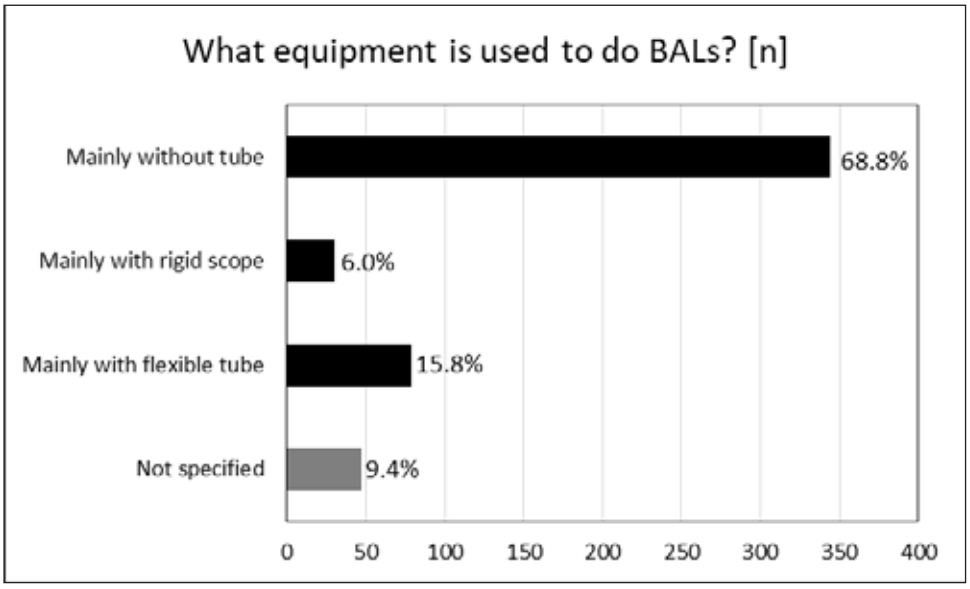

Figure 1. The equipment used for BAL is shown. Given are the number and percentage of participants (n = 500).

Analgosedation and local anesthesia

For the sedation, 76.8% (311/405) of the respondents used propofol and 67.9% (275/405) midazolam. Therefore, many respondents used both drugs, most probably as a combination, while opioids were used by 12.4% (50/405) of the participants.

Local anesthesia for bronchoscopy can be performed in several ways, either as a single mode of application or in combination. Inhalation of a local anesthetic was used by 32.8% (164/500) of participants, spray application of a local anesthetic to the throat by 73.6% (368/500), and instillation of a local anesthetic to the bronchial system by 76.4% (382/500). A total of 60.2% (301/500) reported that the instillation of a local anesthetic to the bronchial system is performed immediately before BAL. There is a marked difference in the general instillation of a local anesthetic to the bronchial system depending on whether an anesthesiologist is present during bronchoscopy (29.8%; 14/47) or not (90.6%; 367/405).

Procedures to instill and recover lavage fluid

More than half (64.4%; 322/500) of the physicians instilled the fluid directly through the working channel, while 22.2% (111/500) used a separate catheter, which was inserted into the working channel (Figure 2a). If the working channel was used directly for instillation and recovery of lavage fluid, 70.2% (226/322) flushed the working channel with saline before application of the first aliquot (Figure 2b).

A major technical variation between the responding physicians was the instilled volume of saline used for BAL. Figure 3 shows what the respondents used as a criterion for their instilled fluid volume. While 202 physicians (40.4 %) used a fixed total amount of instillation volume, 196 (39.2%) physicians reported that the total amount is based on the recovery. In the case where the total amount was based on the instilled volume, the median volume instilled was 100 ml (10% percentile: 100 ml, 90% percentile: 200 ml). If the recovery was used as a criterion for the total instilled amount, the median target recovery volume was 50 ml (10% percentile: 30 ml, 90% percentile: 100 ml). However, the aimed target recovery volume was very low in some cases (minimally 3ml). Independent of this, 43.5% of the physicians defined a minimum amount for the recovery (median = 30 ml). The aliquot volume was usually 20ml (median 20 ml, 10% percentile 20ml, 90% percentile 100ml). After instillation, 61.1% (305/499) of respondents recovered lavage fluid manually and 23.6% (118/499) used mechanical suction of which 5.6% (28/499) used support without reduction of

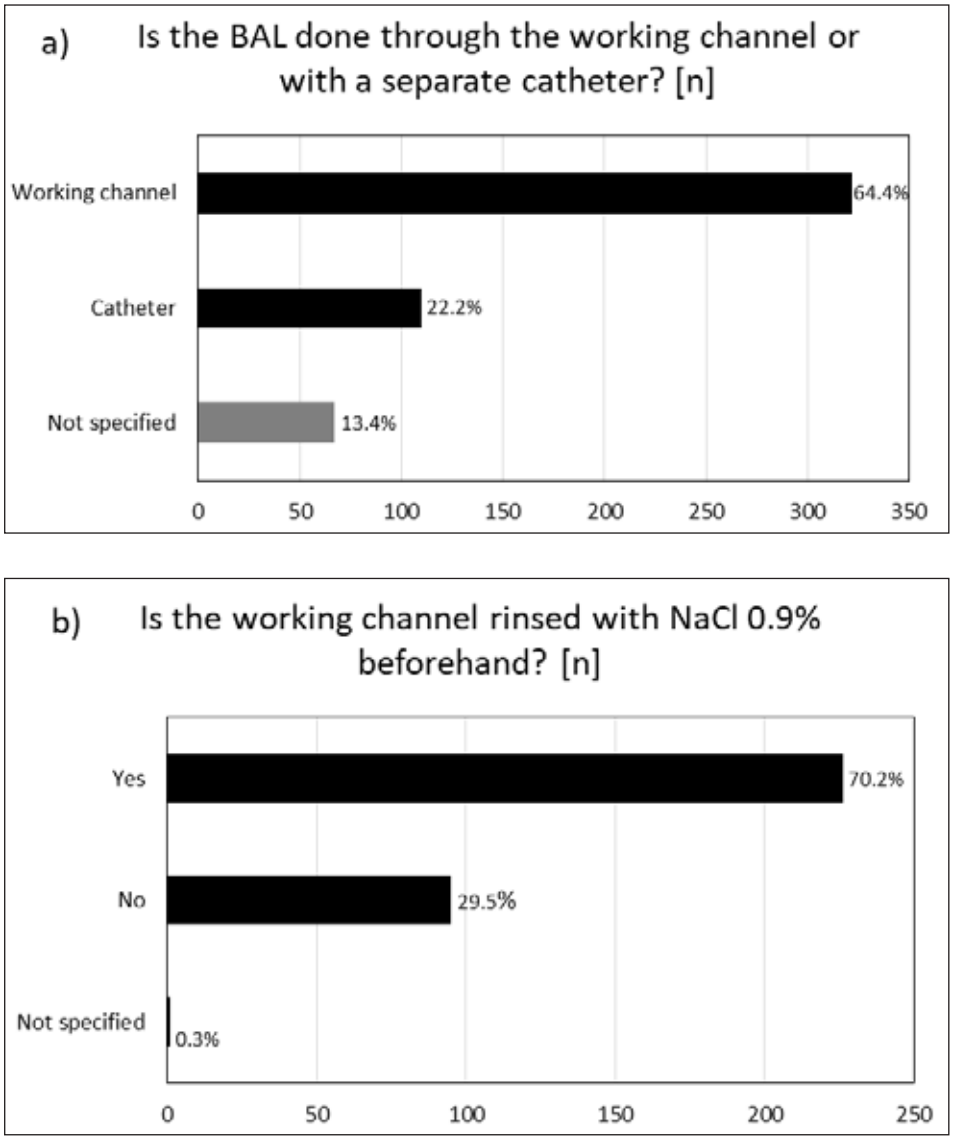

Figure 2. a) Participants were asked whether the BAL procedure is done directly through the working channel or by using a separate catheter. The results are given in number and percentage of all participants (n = 500). b) Of the participants that used the working channel directly, the number and percentage of participants are given that rinse the channel with saline before performing BAL (n=322).

applied negative pressure (Figure 4). The first portion of the lavage aspirate was routinely discarded by a median of 50.0% of bronchoscopists (n = 196), the median volume discarded was 20 ml (n = 164). Slightly less than half (43.5%; 217/499) predefined a minimal recovery volume to indicate a successful BAL (Figure 5). The median predefined minimal recovery was 30 ml.

Site of lavage

In case of diffuse ILD, the middle lobe or the lingula were used as standard sites for BAL by 56.1% (280/499) of respondents, while 26.1% (130/499) performed BAL in those segments with the most prominent interstitial lung abnormalities; 17.8% (89/499) did not respond to this question.

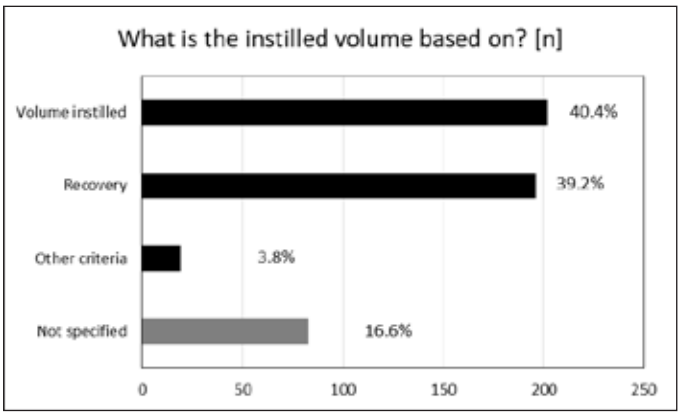

Figure 3. The participants were asked what they base their instilled volume for BAL on. The results are given in number and percentage of participants (n = 500).

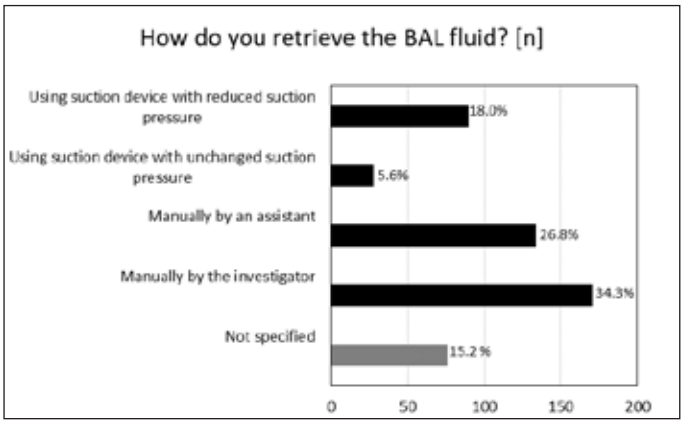

Figure 4. The participants were asked how they retrieve the BAL fluid. Given are the number and percentage of participants (n = 499).

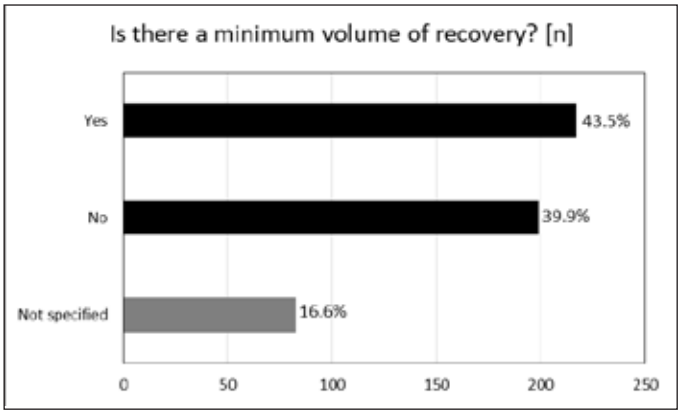

Figure 5. The participants were asked whether they define a minimum recovery volume. Given are the number and percentage of participants (n = 499).

In patients with localized lesions suspicious for organizing pneumonia, inflammatory infiltrates, malignant lesions, or similar, the majority (78.0%; 389/499) performed BAL in the area of greatest abnormality, while only 4.2% (21/499) did not; 17.8% (89/499) did not respond to this question.

Sample transport and cell analysis

In the majority of the cases, BAL was not transported in a special transport medium (no special medium: 61.5%; special medium: 20.6%; not specified: 17.8%). The containers used to collect BAL samples were usually made of plastic (71.5%). Few participants used glass (3.4%). The remaining did not specify (18.8%) or did not know (6.2%). When asked whether BAL was transported on ice, 72.8% said no, while 8.2% said yes.

About 50% of the pulmonology departments had their samples analyzed externally and around 30% in their own institution (see Table 1).

The average time between BAL recovery and the time the sample arrived at the lab was about two hours (mean 115.6 ± 267.0 min.; 95% CI: 86.4-144.9; n = 323). When asked how much time passes between BAL recovery and cytological or immunocytological analysis, 28.5% (data not shown) and 36.5% of the participants, respectively, did not know (Figure 6). The time to cytological or immunocytological analysis was more than 1 hour in 63.3% (data not shown) and 83.3% (n = 210) of the cases, respectively.

Discussion

In the past years, since the 2011 IPF guideline, the scientific interest in the diagnosis of ILDs has focused mainly on diagnostic algorithms, radiologic and histologic criteria, as well as transbronchial cryobiopsies. BAL was not the focus of scientific attention. However, the quality and thus how conclusive BAL data are is crucially dependent on how BAL is technically performed (9). Conferences over the years have repeatedly been held on the BAL procedure including timing, sources of cells, use of findings, and perturbation of BAL components (10). There have been calls for training and standardization. Nevertheless, the ATS guideline on clinical utility of BAL is vague and rarely gives clear instructions on how to implement the procedure (9). The present survey evaluated how BAL is currently performed in Germany. The study showed that in part there are great variations in the technical procedure, which could strongly affect the conclusiveness of the BAL results. We will discuss the different aspects of the study sequentially.

Table 1. Where is the cytological and immunocytological analysis done?

Site of analysis	Cytology [n]	Immunocytology [n]
Internally at hospital	171(34.3%)	134(26.9%)
Externally	229(45.9%)	251(50.3%)
Not done	1(0.2%)	14(2.8%)
Not specified	97(19.4%)	99(19.8%)
Unknown	1(0.2%)	1(0.2%)

Technical requirements for BAL

Guidelines only report on performing BAL in the setting of a flexible bronchoscopy (9,11). Studies analyzing the impact of doing BALs through a rigid bronchoscope or through a flexible tube are missing. However, as "rigid" usually means using a flexible bronchoscope through a rigid scope, an impact of a rigid conduit or a tube on the quality and results of the BAL is unlikely. Neither a rigid scope nor an intubation with a tube is necessary to perform a BAL, and the setting should be chosen based on other procedures planned during the bronchoscopy such as transbronchial cryobiopsy or endobronchial ultrasound (EBUS). Based on the survey, it cannot be concluded whether patients were intubated for the procedure, i.e. with a flexible tube, or if the procedure was performed in patients who were intubated for other procedures done during the same bronchoscopy.

Analgosedation and local anesthesia

According to the survey results, BAL is most frequently executed without an anesthesiologist in moderate sedation using a combination of propofol and midazolam. Performing BAL under general anesthesia yields similar results to local anesthesia (11). Although there are recommendations on sedation during bronchoscopy (12), no recommendation on the optimal drugs for sedation has been given

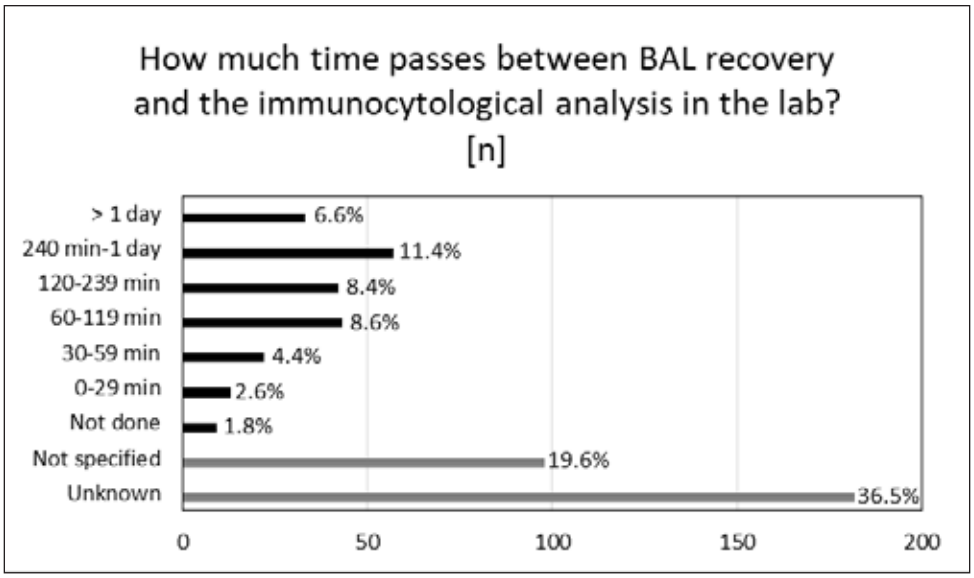

Figure 6. The participants were asked how much time passes between BAL recovery and immunocytological analysis. Given are the number and percentage of participants (n =499).

to date. More important than the choice of specific drugs is that sedation is deep enough to prevent coughing, which would have a negative effect on cell recovery and contamination with bronchial secretions and especially blood (13).

An interesting finding of the present study is that roughly 1 out of 5 physicians routinely perform the BAL in the presence of an anesthesiologist. Whether this has a direct impact on patient outcome (i.e. higher safety standards) has not been conclusively investigated so far. However, it can be assumed that the presence of an anesthesiologist is not primarily motivated by the BAL, but by other factors such as an additional cryobiopsy. We assume that performing BAL is only a minor burden for the patients. Therefore, with sufficient pulmonary resources, no special precautions (e.g. the presence of an anesthesiologist or intubation) have to be taken. At the same time, the consumption of health care resources rises markedly if an anesthesiologist is routinely involved in bronchoscopy – especially given the fact that under these circumstances additional personnel is involved on top of the specialist (e.g. specialized nurses).

This study highlights that in the vast majority of bronchoscopies propofol is used for sedation and can be considered the (informal) standard medication for sedation in Germany. Only a minority (about 12%) routinely apply analgesics (i.e. opioids) during bronchoscopy.

According to the present study, inhalation of local anesthetics is rarely performed. In contrast, the application of these agents to the throat and the bronchial system must be viewed as standard. Uncertainty remains whether there is a clinically meaningful impact of local anesthetic application with regard to BAL quality/interpretation (i.e. bacterial death/cell destruction). Duddridge et al. report that lidocaine at concentrations of 1.5% and 4% show negligible effects on BAL metabolic activity if the supernatant is not removed promptly from the harvested cells (14). Interestingly, the presence of an anesthesiologist results in markedly reduced application of local anesthetics to the bronchial system. This is most likely explained by the fact that in contrast to pulmonologist-guided bronchoscopies including analgosedation, patients receive muscle relaxants during (rigid) bronchoscopy if anesthesiologists are involved. However, these points are not addressed in the current guideline (9).

Procedures to instill and recover lavage fluid

Taking into account that the European Society of Pneumology (one of the two founding societies of the ERS) published its recommendations as early

as 1989, there is a surprising degree of heterogeneity in instillation and recovery procedures. While these guidelines recommend instillation through the working channel of the fiberoptic bronchoscope (11), 22% of respondents use a separate plastic catheter. The guidelines also address the containers in which the recovery fluid is collected. Ones without silicone coating and some plastic containers promote cell adherence to the container surface and thus may influence the BAL result (9). However, to date, to the authors' knowledge, no data are available on the adherence of recovered cell types to the plastic surface of these separate plastic catheters. The guideline for the performance of BALs does not clearly define the criterion, which should be used as an orientation for the instilled volume. Although an instilled volume of 100-300 ml is recommended, at the same time a minimal recovery of more than 30% is considered sufficient. With a recovery smaller than 10%, the BAL is considered inconclusive (9). In the present study, only 40% chose a predefined fixed amount of instillation volume. Thirty-nine percent used a variable amount based on the recovered volume. Interestingly, the predefined instilled volume was less than 100 ml in 3.9% and thus falls below the recommended lower limit. In 51%, the aimed instilled volume corresponded to the suggested minimal amount of 100 ml. It is possible that some physicians, who use the fixed amount of instillation volume, adapt this during bronchoscopy to higher volumes when they notice that the recovery would be too low.

Interestingly, a great technical variation is found in the predefined target recovery volume. Costabel et al. recommend recovering at least 25 ml of the instilled saline (15). The Clinical Practice Guideline of the ATS from 2012 recommends that the minimal total volume retrieved should be greater or equal to 5% of the instilled volume, i.e. 5-15 ml (optimal sampling retrieves >30%) (9). In the present survey, only 0.5% fall below the lower limit of 10 ml defined in the guideline. The median sought recovery volume was 50 ml. However, the described lower limit in the guideline should be evaluated critically. If 20 ml portions are used and the recovery is merely 10% per portion, it would mean that when performing BALs through a working channel (volume of the working channel about 2 ml) only fluid from the working channel would be aspirated. This fluid would not have had contact with the bronchial system let alone with the alveolar region. Accordingly, we consider the recommendation of a recovery of more than 50 ml (50-60 % of the instilled volume) given by Costabel as a good orientation (15).

Should we discard the first portion? According to Klech and Pohl (11) the first aspiration may be significantly different from the subsequent ones due to the high proportion of bronchial washing. This is especially relevant in cases with bronchial inflammation or mucus contamination. In the present survey 43.5% of the physicians reported that they discard the first aspirate. However, to the authors' knowledge, no data are available on this topic so far. The instilled aliquots are usually 20 ml (11). In the European recommendation from 1989, an aspirate after each instillation is suggested (11). However, there are no data that instillation of the first 60 or 80 ml as a single portion might be better because the large alveolar bed cannot be reached with the first 20 ml. It should be discussed whether the danger of repeated "bronchial washings" might be increased. Unfortunately, data on this topic concerning BAL are still lacking. Regarding recovery, several respondents use manual suction, which is also suggested in the European recommendations. However, 6% use mechanical support without reduction of negative pressure, which should be avoided.

Site of BAL

The preferred site of BAL by the majority of respondents reflects existing recommendations. The Report of the European Society of Pulmonology Task Group on BAL (11) recommends a standard site of sampling in diffuse interstitial lung disease, preferably the middle lobe or the lingula. The reason is that approximately 20% more fluid and cells can be recovered from these lobes than from the lower lobes (16). Based on the data available at the time of publication, the task forces summarized that, in general, lavage at one site would give sufficient clinical information and may be considered representative of the whole lung (11). Most respondents in the current survey follow this approach. Yet, in contrary, a more recent ATS clinical practice guideline (9) suggests that the lavage site should be chosen on the basis of the results of a high-resolution computed tomography performed before bronchoscopy. This is

Table 2. Recommendations for the transport of the recovered BAL fluid according to Meyer et al. (6)

(1)	The BAL recovery should be collected in containers that prevent cells from adhering to the vessel wall. Otherwise, cell loss could result (e.g. silicon coated glass containers or containers made of polypropylene or plastic containers especially developed for cell culture) (7).
(2)	BAL samples may be transported at room temperature if the analyzing laboratory is in the same hospital and there is no transport delay.
(3)	If the expected transport time is up to one hour, the material can be sent in its native form, but on ice (4° C). It is important to ensure that the transport fluid does not freeze.
(4)	If the expected time of transport is more than one hour, the material should be transferred to a nutrient solution. Media for cell culture are suitable (i.e.: MEM+25 mM HEPES). In case the transport is at room temperature, the addition of a bacteriostatic agent to the culture medium can be considered (i.e. 0.1ml Pen/Strep). This, for example, makes postal shipping over 24 h possible without cooling [12].
(5)	If the analyzing laboratory cannot work up the native sample immediately, it is recommended to transfer it to a culture medium. The sample should be cooled until it is worked up, which should not be more than 24 h.

preferable to a "traditional" BAL site (i.e. the middle lobe or lingula) based on low evidence data suggesting superior results if a lavage is performed in areas with more extensive parenchymal change. However, since then, no further higher-grade evidence has been generated reflecting this recommendation. With localized lesions, the majority of respondents chose the area with the most prominent changes for lavage, which reflects the recommendations by the European task group report (11).

Sample transport and cell analysis

Although over 70% of the hospitals transport BAL without cooling and the majority without special transport medium, about half the samples are processed externally. The average transport time to the analyzing laboratory is about 2 hours. Many participants did not know how long it takes until their samples are cytologically and immunocytologically analyzed. This means that the BAL fluid is often transported under poor conditions. Without cooling and special nutrients, the cells already begin to deteriorate and die after 60 minutes (17). The correct transport is essential to preserve the quality of the BAL cells. Therefore, it is important to ensure optimal transport so that the quality of the cells is as good as possible. The diagnostic evaluation is strongly dependent on the preservation of the original material. Table 2 summarizes the recommendations for the sample transport.

However, not only the transport is important, but also how BAL is processed and evaluated in the laboratory. This influences the quality of the analysis and thus the accuracy of the results.

Conclusions

The present study demonstrates the broad heterogeneity of how BAL is performed in Germany. Some variations, however, should clearly be considered questionable, because they have a negative effect on the conclusiveness of the BAL (e.g. recovery volume, type and duration of sample transport). Thus, even for the "simple examination" BAL there is a need for training. Other variations are the result of missing standardizations (e.g. a broad range of recommended total instilled volumes: 100-300 ml). Such a standardization, even though it is often based on expert opinion, is highly warranted and would establish a basis for future comparative studies to optimize the BAL method. Although it is almost certain that variations in performing BAL are also seen in other European countries, further studies beyond Germany would underline the urgency for standardization and training further.

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