Review Article

The use of aerosol generating procedures (AGPs) during the COVID-19 pandemic in the diagnosis of lung cancer: a narrative review

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Objective: In this article we discuss the current evidence for these concerns and highlight where further work is required to understand the risk from these procedures and how it can be mitigated for.

Background: The COVID-19 (coronavirus-19 or SARS-CoV-2) pandemic has impacted on many aspects of patient care both for those with the virus and those with other illnesses. Of particular concern has been the risk to staff and patients from the spread of the virus in health care settings. This has led to changes in guidelines and practice in community and hospital settings that has implications on patient diagnostic pathways in lung cancer, with a specific emphasis on aerosol generating procedures (AGPs).

Methods: A literature search was carried out and 44 abstracts were initially found. Given the novel status of COVID-19, we included severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS) in our search. Five papers were selected for further analysis. An additional paper was highlighted during our research and therefore included in our review.

Conclusions: The papers selected assessed the risk of transmission during AGPs. The six articles selected assessed the risk of aerosol transmission during various AGPs (bronchoscopy, pleural procedures and pulmonary function tests) and each found that the risk of viral transmission via aerosol was low. As mentioned above, at the time the paper was written, there was a paucity of evidence regarding AGPs in the era of COVID-19. There is emerging evidence that our understanding of these procedures may be outdated and the risk of transmission maybe lower than previously anticipated. However, we need further reliable evidence to change practice going forward.

Keywords: Aerosol generating procedures (AGPs); COVID-19; bronchoscopy; lung function tests; pleural procedures

Received: 20 February 2021; Accepted: 13 July 2021; Published: 25 September 2021.
doi: 10.21037/med-21-16
View this article at: https://dx.doi.org/10.21037/med-21-16

Introduction

SARS-CoV-2 or COVID-19 is a novel coronavirus which has caused a pandemic for over a year (1). COVID-19 continues to affect millions of people due in large part to its ability to spread from person to person (2). As of 16 February 2021, the UK has reported 4,058,468 positive cases (3) and 129,498 deaths with COVID-19 on the death certificate (4). This has had a major impact and strain on society, in particular health care delivery worldwide (5). There have been major implications for health care systems

as they attempt to treat patients infected with the virus but also continue managing other diseases such as cancer. Throughout the pandemic, hospitals have continued their cancer services whilst maintaining safe practices in order to mitigate the spread to patients and health care professionals (HCPs). Public Health England (PHE) have published guidelines regarding different levels of personal protective equipment (PPE) and other precautions depending on COVID risk pathways to reduce the risk of spread between patients and to HCPs (6).

These extra measures have important implications for lung cancer diagnosis and treatment pathways. The majority of cancer treatment requires a tissue diagnosis, with the development of targeted biologic and immunotherapy for lung cancer necessitating the need for larger more complex sampling. In many cases this requires endoscopic and pleural procedures to provide such samples. In addition, these cancer treatment pathways also require assessment of a patient's fitness via lung function testing, adding to the risk of viral spread.

Aerosol generating procedures (AGPs) are defined by the World Health Organisation (WHO) as those which lead to the generation of airborne particles (7); specifically, particles <5 micrometer (μm) in size. These have the propensity to remain suspended in the air for prolonged periods of time and therefore remain present in the environment to cause infection. This definition of an AGP means that many different medical procedures can be considered as an AGP without defining their actual risk to HCPs and other patients. It also overlooks larger particles and droplets which may not remain suspended in the air but can spread the virus. Both droplets and AGP can land on surfaces and remain in the clinical environment for extended periods of time leading to the risk of viral spread. The key therefore is to identify those procedures that are associated with greater risk and attempt to limit that. This subset of techniques, which includes bronchoscopy, are deemed to be "high risk AGP" as they are considered more likely to cause the spread of infections by increasing the number of respirable particles.

The most recent guidance published on 21 January 2021 from PHE lists a number of AGPs including bronchoscopy which are 'associated with an increased risk of transmission' (7). For AGP in these patients, they recommend airborne transmission PPE which includes single use disposable gloves, single use full gown, FFP3 or respiratory hoods and single use or re-usable eye/face protection.

In this article we set out the current guidance for AGP use during the COVID-19 pandemic along with the evidence base behind these statements.

We present the following article in accordance with the Narrative Review reporting checklist (available at: https://dx.doi.org/10.21037/med-21-16).

Current advice on procedures

Bronchoscopic procedures

This section covers multiple similar techniques, including flexible, rigid, interventional and endobronchial ultrasound bronchoscopic procedures, as they all require intubation of the trachea and airways. In so doing, they trigger coughing and aerosol/droplet generation. Several national societies, including the British Thoracic Society (BTS) (8) and the American Association for Bronchology and Interventional Pulmonology (AABIP) (9) have published statements on the use of these procedures during the COVID-19 pandemic, which rely heavily on expert opinion. Their guidance includes several key practical themes for clinicians to consider including:

(I) Ensuring that there is no alternative strategy that could provide similar diagnostic yield before undertaking a bronchoscopy;
(II) Maintaining strict adherence to PPE throughout the procedure. This includes the use of FFP3 masks, eye protection, full gown and glove coverage for all staff members;
(III) Careful identification of appropriate patients. This includes swabbing patients 48 hours prior to any procedure for COVID-19 and ensuring they self-isolate from the point of referral;
(IV) Reassessment of symptoms within 1 working day of the procedure to ensure no new symptoms or COVID-19 contact;
(V) Only essential staff present in bronchoscopy suite during time of procedure.

The Antimicrobial Resistant and Healthcare Associated Infection (ARHAI) Scotland released a document in October 2020 looking at the evidence base for medical procedures which pose a higher risk of respiratory infection transmission from patients to HCPs. It found there was little evidence (of which was weak) looking at the transmission of respiratory viruses during bronchoscopy; however, it was included in the list due to 'historic expert opinion' (10).

Pleural procedures

Pleural procedures are crucial for the diagnosis and symptomatic management of cancer. These procedures include diagnostic and therapeutic pleural aspirations, intrapleural catheters (IPCs) and thoracoscopy. The BTS has published guidance (last version 21 May 2020) regarding ongoing pleural services during the pandemic (11). Again, this document was based on pleural expert advice given the paucity of evidence in this area.

Patients with symptoms consistent with COVID-19 or who have confirmed COVID-19 should have their procedures delayed. Patients with elective pleural procedures should have a nasal or oropharyngeal swab 48 hours prior to the procedures. With regards to PPE, they have suggested level 1 PPE for 'closed' pleural procedures (pleural aspirations and chest drains) and level 2 PPE for 'open' procedures (thoracoscopy and IPC insertion) despite these not being listed as AGPs (12).

Pulmonary function testing

PHE have not listed pulmonary function tests (PFTs) as AGPs. However, it is recognised that respiratory droplets are generated during these procedures due to patient coughing. The European Respiratory Society (ERS) and Association for Respiratory Technology and Physiology (ARTP) COVID-19 group have both published updates recommending the use of PPE when undertaking PFTs (12-14) and should only be undertaken if necessary (i.e., it will confirm or change patient's outcome). ESR has further recommended that PFTs should not be performed for a minimum of 30 days post infection (13).

There also needs to be consideration regarding adequate air circulation in the testing department which will limit the number of cases being performed (14).

Structure literature review methodology

The literature search was undertaken on 17 February 2021. The databases used included EMBASE, CINAHL, EMCARE, Medline and PubMed. The following terms were included: 'aerosol generating', 'bronchoscopy', 'pleural procedure', 'pulmonary function test' OR 'lung function tests. Along with the terms 'COVID-19', 'SARS-CoV-2', 'severe acute respiratory syndrome' 'coronavirus 2019', we decided to incorporate studies which included severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS) to widen our search. We did not have a time limit on the search but excluded papers which were not written in English and conference abstracts. A breakdown has been included in the Supplementary file (Figure S1).

Forty-four abstracts were found. Of these 23 were excluded as they did not mention bronchoscopy, pleural procedures or PFTs in the abstract. Two abstracts were excluded as they were paediatric studies. Fourteen abstracts were excluded as they were guidelines, anecdotal papers recalling clinicians' experience of AGPs during COVID or unsuitable study design. Five were selected for further analysis. A flow diagram to depict this has been included (Figure S2).

Two of these studies are systematic reviews looking at all AGPs and the risk of transmission to HCP. They both identified the same two papers examining the risk of SARS to HCP during bronchoscopy, we therefore analysed those two directly as well.

A further study was published after the initial write-up which has added some relevant information; we have therefore included this in our analysis below.

Studies included

Table S1 showing a brief summary of studies selected can be found in the Supplementary file (Appendix 1).

Doggett, et al. Characterization of experimental and clinical bioaerosol generation during potential aerosol-generating procedures (15)

This study set out to characterise the number and size of aerosols produced during tracheal intubation and bronchoscopy, initially in an animal model (pigs) and then humans, in an elective outpatient setting. They performed 16 intubations on the animal models. The pigs were sedated and then anaesthetised. The aerosol generation was measured 10 seconds pre-, peri- and post intubation. They did not find a statistically significant increase in aerosol production in any size category. In fact, they found a small decrease in 0.3 µm particles during intubation compared to the baseline. They went on to perform 49 elective bronchoscopies under procedural sedation. The procedures were performed in negative pressure rooms and all staff wore PPE. They measured the particles 100 seconds pre-procedure, during and 100 seconds post-procedure. Ten were excluded from analysis due to technical issues.

Eighteen/39 procedures (46%) showed increased aerosol

production in 0.3 µm, 1/39 (2.6%) and 2/39 (5.1%) increase compared to baseline for 1.0 µm and 5.0 µm size particles. However, when analysed as a group, they did not find a significant difference in aerosol production of 0.3 µm particles, however a measurable increase was observed in four cases. Overall, there was significant decrease in aerosol production of 1.0 µm particles and 5.0 µm particles at both sites (P<0.01 and P<0.0001 respectively). The data was further analysed to identify aerosol generation at specific procedural points (scope insertion, coughing etc.). They found that both suction (P=0.10) and bronchoalveolar lavage (P=0.11) were associated with increased aerosol production of small particle size, but neither were statistically significant. Their findings seem to suggest that risk of aerosol production is not as severe as previously thought. Several limitations were identified by the authors including interpatient variation, exclusion of urgent and less controlled procedures and choice of optical particle counter. Although this study helped quantify number and size of aerosols produced during bronchoscopy, it did not explore the risk of transmission to HCPs or investigate the spread of larger droplet sizes.

Chang et al. Safety and effectiveness of bronchoscopy in critically ill patients with coronavirus disease 2019 (16)

This was a single centre retrospective study carried out in New York. The primary outcomes were patient and staff safety during bronchoscopy of intubated patients, which were described as absence of immediate periprocedural complications and viral transmission. Of the 321 patients who required intubation and ventilation due to COVID-19, 107 underwent bronchoscopy. In total, 241 bronchoscopies were carried out during the study period of 42-day period. All patients received periprocedural anaesthesia and staff wore full PPE. The team comprised of ten bronchoscopists, one of whom had already contracted COVID-19 before performing any procedures and was therefore excluded from the study. The nine remaining members tested negative for COVID-19 via nasal pharyngeal swab. On average, each provider performed 42 bronchoscopies. Whilst this study yielded positive results, the bronchoscopies were carried out in patients who were sedated and apnoeic during the procedure removing a part of the aerosolising risk to staff. This therefore cannot be extrapolated to an outpatient setting. They also did not mention whether there were additional nursing staff to assist during the procedure, and if present, whether there were any COVID-19 positive results.

Duffy et al. Chest drain aerosol generation in COVID-19 and emission reduction using a simple anti-viral filter (17)

This study was carried out to determine whether a bubbling chest drain is aerosol generating and whether this can be controlled with the use of an anti-viral filter. As mentioned above, pleural procedures are not considered aerosol generating but the author noted this was due to lack of prior evidence. They set up a chest drain with an underwater seal in a 60-L plastic box and the drain tubing was attached to a medical air cylinder via an airtight conduit in the wall of the box. They placed a particle counter inside the box and measured number and size of particles within six channel sizes. They initially counted the particle concentrations in the air surrounding the chest drain for 20 minutes as a baseline measurement. Air was then pumped through the circuit for 20 minutes at 1 L/min, then the air was switched off allowing baseline conditions to re-stabilise for a further 20 minutes. At the end of the 60 minutes the measurements were recovered. This was repeated at different air flows and was repeated after applying the air filter. The results showed that particle emissions increased with increased air flow; the largest increase was noted in smaller particles (0.3–3 µm) by 700, 1,400 and 2,500 pc/ft^3 at 1, 3 and 5 L/min. They found that particles in the aerosol range (<5 µm) were generated by a bubbling chest drain at continuous flow rates of at least 1 L/min. Whilst this finding was statistically significant, there were limitations. This procedure was carried out only once and not repeated. This was in a controlled setting which is vastly different to the airflows of a normal ward environment. Furthermore, this is only applicable to pneumothorax drainage, not effusions (which are more commonly associated with cancers).

Raboud et al. Risk Factors for SARS transmission from patients requiring intubation: a multicentre investigation in Toronto, Canada (18)

This was a retrospective cohort study looking at the Toronto SARS outbreak. Its aim was to identify risk factors associated with transmission of SARS-CoV from patients to HCPs, in particular looking at risk of transmission associated with 'high-risk procedures'. Six hundred and twenty-four HCPs who provided care to 45 patients with

confirmed SARS, participated in the study. These HCPs performed a range of procedures, some of which were AGPs. Ten HCPs were involved with bronchoscopic procedures. Of these ten, none were diagnosed with SARS. We do not know what their roles were during the procedure or what level of PPE was worn. Without this information, it is difficult to make an assessment on how significant the above is. Another limitation involves the questionnaire the HCPs were asked to complete (via face-to-face or telephone interviews); the interviews were completed at a median of 4.2 months (range, 0.2–10 months) which allows for recall bias.

Loeb et al. SARS among critical care nurses, Toronto (19)

This retrospective cohort study was conducted to examine the rate of transmission of SARS amongst nurses who worked in two critical care units in a Toronto hospital. They propose that 'patient care activities that increase exposure to respiratory droplets' are associated with increased risk of SARS transmission. Thirty-two nurses were included in the study. Two nurses participated in bronchoscopy, one of whom was found to contract SARS. Again, we do not know what role the nurse who contracted SARS played during the bronchoscopic procedure and what level of PPE she was wearing. The study felt 'high risk activities' were intubation and suctioning before intubation; we do not know if the infected HCP participated in any of these activities which lead to the transmission of SARS. Without more information and a small sample size, it is difficult to know the significance of this finding. The same issue of recall bias also applies.

Sheikh et al. Risk and mitigation of aerosolization from lung function testing: results from the AERATOR study (20)

The authors identified the discrepancy between different expert groups and medical bodies. They therefore set out to identify the risk of AGPs during lung (or pulmonary) function testing by measuring aerosol emission from volunteers when performing spirometry compared to them breathing, speaking and coughing. They also assessed the effectiveness of mitigation measures such as mouthpiece filters. They used 33 healthy volunteers with normal lung function. They found that voluntary cough produced on average a higher number of particles. Peak flow then produced approximately half of that at 0.76 particles/cm^3/sample. They also found that using a filter on the peak flow device reduced aerosol emission to 0.09 particles/cm^3/sample. They concluded that peak flows do not generate significant aerosol when compared to cough and adding a filter reduces the number of emissions further. Whilst the results are promising, there are some limitations to this study. Principally, the authors demonstrated voluntary cough is associated with an elevated aerosol emission. Spirometry is known to provoke a cough in patients, even in those without pre-existing cough (21). Involuntary coughing may produce more aerosols due to the sheer force and duration of cough, something which may be difficult to predict. So, whilst the procedure itself may be safe from aerosol spread between HCPs and patients, one must consider the involuntary coughing which is induced during this procedure and the risk this carries. This paper however has yet to be peer reviewed.

Discussion

COVID-19 infection rates remain high in the UK. NHS services as a whole are generally still operating at reduced capacity however cancer diagnostics have needed to continue as previously with additional precautions. This presents a particular concern in respiratory cancer diagnostics owing to the common site of COVID-19 infection.

As highlighted above, there are multiple procedures which are pertinent for the diagnosis and management of lung cancer. Bronchoscopy is considered an AGP and has been discussed at length in review articles and guidelines. However, the paucity of robust evidence regarding bronchoscopy and risk of COVID-19 transmission to HCP leads to anxiety among staff but also limits the efficiency of any service as restrictions are placed on its use. From our literature review, there are multiple abstracts with recommendations and expert consensus regarding bronchoscopy in the era of COVID-19. The overall message from these papers reinforces the use of full PPE, careful consideration regarding need for such procedures, and use of alternative imaging modality to confirm diagnosis. However, given the importance of obtaining tissue for histological diagnosis, bronchoscopy cannot be avoided. This is a problem faced worldwide. A commentary from the respiratory team at a tertiary hospital in Malaysia found that the number of procedures they were carrying out had significantly fallen. They postulated this may be due to reduced movement due to their interstate travel restrictions, avoidance of healthcare services from patients and

seeking alternative measures to obtain diagnoses to avoid spread (22). They also reported anxiety amongst the staff initially regarding the potential spread during AGPs; they found with formal guidelines and information regarding donning/doffing and social distancing eased some concerns.

Larger studies are required to look at the rate of aerosol generation in an outpatient diagnostic setting, paying particular attention to which steps exactly create the greatest number of particles. We also need to look at the subsequent rate of transmission to HCPs and how we can manage these risks. Current studies have also focused on AGP's using particle counters. These devices collect AGP of a given size at a specific distance from a patient. This process overlooks larger droplets that are not suspended in the air but will still spread through a room. Cough models in surgical theatre environments have shown that in both conventional and laminar flow environments larger fluid drops can be coughed great distances (23). Therefore, to give a complete understanding of the risks posed to patients and HCPs' future, studies need to incorporate both AGP's and larger droplet spread.

Pleural procedures and PFTs have not been studied as extensively and are currently not classified as AGPs. The study by Duffy *et al.* (17) found that aerosol particles were generated by a bubbling chest drain and increased air flow led to an increase in particles released. Whilst these findings are more relevant to patients with pneumothoraces, chest drains (+/– talc pleurodesis) and IPCs are more commonly used to treat malignant pleural effusions and recurrent effusions. A case series by Lescure *et al.* (24) followed five patients with COVID-19; one of whom developed an exudative pleural effusion with SARS-CoV-2 detected in the sampled pleural fluid. Whilst pleural effusions are an uncommon finding in primary COVID-19 disease (25), the rate of pleural infectivity is not well known. It is therefore pertinent to clarify whether chest drain, or IPC insertion is associated with aerosol generation for patients with pre-existing effusions who are infected by SARS-CoV-2.

As with pleural procedures, there is a gap in knowledge regarding the risk of transmission of COVID-19 in patients undergoing spirometry. A regional Canadian consensus was published in 2020 (26) with recommendations for restoring PFTs in the community. During their literature search, they found no large robust study looking at aerosol generation during spirometry but made recommendations based on expert opinion and previous guidelines. Again, larger studies addressing these gaps would help provide a more efficient service for the current and future respiratory viral pandemics.

Interestingly, Hamilton *et al.* (27) published an article in the *Lancet Respir Med* proposing a rethink about the term AGPs as a binary term as the risk of aerosol production from these procedures alone remained low. Whilst this is true, we know from experience and expert guidance that a consequence of these procedures is coughing which known to produce more aerosols. This is unfortunately unavoidable and therefore these procedures are still considered high risk/AGP.

Conclusions

The current guidance available for the use of AGP in clinical practice during the COVID-19 pandemic is biologically plausible but based on limited clinical evidence. These procedures remain frequent and important but result in a more complex and often delayed pathways. Further larger studies would be helpful to provide a clear understanding of the risks to staff and patients and importantly how they can be reduced whilst maintaining efficiency. Until we have a greater evidence base it is likely that we will need to continue relying on poorly evidenced guidelines, something that may lead to unnecessarily delays and poorer outcomes for our patients.

Acknowledgments

Thanks to RH, clinical librarian at the QuAD Centre at the Queen Alexandra Hospital.
Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Giuseppe Banna and Alfredo Addeo) for the series "Changes in management of mediastinal tumours following the surge of COVID-19 pandemic" published in *Mediastinum*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at: https://dx.doi.org/10.21037/med-21-16

Conflicts of Interest: All authors have completed the

ICMJE uniform disclosure form (available at: https://dx.doi.org/10.21037/med-21-16). The series "Changes in management of mediastinal tumours following the surge of COVID-19 pandemic" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/med-21-16
Cite this article as: Vythilingam S, Quint M, Newsom R, Hicks A. The use of aerosol generating procedures (AGPs) during the COVID-19 pandemic in the diagnosis of lung cancer: a narrative review. Mediastinum 2021;5:29.

HDAS Export
Search Strategy aerosol procedure COVID

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Strategy 981809

#	Database	Search term	Results
1	EMBASE	("aerosol generating" OR bronchoscopy OR "pleural procedure*" OR "pulmonary function test*" OR "lung function test*").ti,ab	62278
2	EMBASE	("severe acute respiratory syndrome" OR "covid 19" OR "SARS-COV-2" OR "n-Cov-19" OR "SARS" OR "MERS" OR "Coronavirus 2019").ti,ab	107284
3	EMBASE	(1 AND 2)	633
4	EMBASE	(transmission).ti,ab	423664
5	EMBASE	(3 AND 4)	233
6	EMBASE	(rate* OR risk).ti,ab	6522659
7	EMBASE	(5 AND 6)	189
8	CINAHL	("aerosol generating" OR bronchoscopy OR "pleural procedure*" OR "pulmonary function test*" OR "lung function test*").ti,ab	7583
9	CINAHL	("severe acute respiratory syndrome" OR "covid 19" OR "SARS-COV-2" OR "n-Cov-19" OR "SARS" OR "MERS" OR "Coronavirus 2019").ti,ab	9065
10	CINAHL	(8 AND 9)	117
11	CINAHL	(transmission).ti,ab	40543
12	CINAHL	(10 AND 11)	61
13	CINAHL	(rate* OR risk).ti,ab	1159325
14	CINAHL	(12 AND 13)	53
15	EMCARE	("aerosol generating" OR bronchoscopy OR "pleural procedure*" OR "pulmonary function test*" OR "lung function test*").ti,ab	9710
16	EMCARE	("severe acute respiratory syndrome" OR "covid 19" OR "SARS-COV-2" OR "n-Cov-19" OR "SARS" OR "MERS" OR "Coronavirus 2019").ti,ab	30035
17	EMCARE	(15 AND 16)	202
18	EMCARE	(transmission).ti,ab	70043
19	EMCARE	(17 AND 18)	82

https://dx.doi.org/10.21037/med-21-16

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20	EMCARE	(rate* OR risk).ti,ab	1464647
21	EMCARE	(19 AND 20)	67
22	Medline	("aerosol generating" OR bronchoscopy OR "pleural procedure*" OR "pulmonary function test*" OR "lung function test*").ti,ab	35404
23	Medline	("severe acute respiratory syndrome" OR "covid 19" OR "SARS-COV-2" OR "n-Cov-19" OR "SARS" OR "MERS" OR "Coronavirus 2019").ti,ab	107905
24	Medline	(22 AND 23)	576
25	Medline	(transmission).ti,ab	377234
26	Medline	(24 AND 25)	227
27	Medline	(rate* OR risk).ti,ab	4679716
28	Medline	(26 AND 27)	183
29	PubMed	("aerosol generating" OR bronchoscopy OR "pleural procedure*" OR "pulmonary function test*" OR "lung function test*").ti,ab	39425
30	PubMed	("severe acute respiratory syndrome" OR "covid 19" OR "SARS-COV-2" OR "n-Cov-19" OR "SARS" OR "MERS" OR "Coronavirus 2019").ti,ab	115328
31	PubMed	(29 AND 30)	652
32	PubMed	(transmission).ti,ab	547538
33	PubMed	(31 AND 32)	362
34	PubMed	(rate* OR risk).ti,ab	5353070
35	PubMed	(33 AND 34)	255

Figure S1 Search strategy.

https://dx.doi.org/10.21037/med-21-16

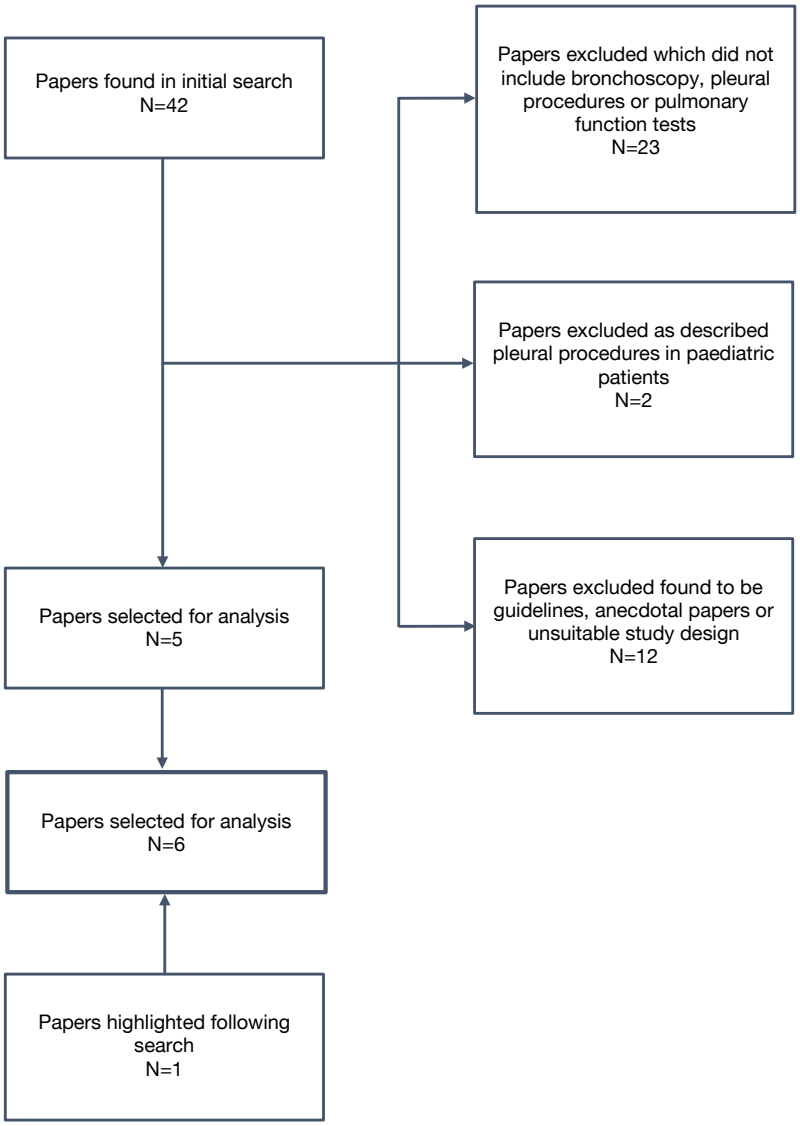

Figure S2 Literature inclusion methodology.

https://dx.doi.org/10.21037/med-21-16

Table S1 summary of studies selected

Study	Study design	Aim	Population
Doggett *et al.* (15)	Observational study	Characterise the number and size of aerosols produced during tracheal intubation and bronchoscopy	16 animal studies and 49 human procedures
Chang *et al.* (16)	Retrospective review	Measure patient and staff safety during bronchoscopy of intubated patients	241 bronchoscopies performed on 107 patients by ten clinicians
Duffy *et al.* (17)	Observational study	Determine whether bubbling chest drain is aerosol generating	N/A
Raboud *et al.* (18)	Retrospective cohort	Transmission of SARS to HCPs from intubated patients	624 in total; ten participated during bronchoscopic procedure and none of these HCPs infected
Loeb *et al.* (19)	Retrospective cohort	Transmission of SARS to ICU nurses	32 nurses participated in study; two were involved in bronchoscopic procedures and one contracted SARS
Sheikh *et al.* (20)	Observation study	Identify risk of AGPs during PFTs by measuring aerosols in healthy volunteers	33 healthy volunteers in total

SARS, Severe Acute Respiratory Syndrome; HCPs, health care professionals; AGPs, aerosol generating procedures; PFTs, pulmonary function tests.

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