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Review

Aerosol-generating procedures and infective risk to healthcare workers from SARS-CoV-2: the limits of the evidence

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S U M M A R Y

The transmission behaviour of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is still being defined. It is likely that it is transmitted predominantly by droplets and direct contact and it is possible that there is at least opportunistic airborne transmission. In order to protect healthcare staff adequately it is necessary that we establish whether aerosol-generating procedures (AGPs) increase the risk of transmission of SARS-CoV-2. Where we do not have evidence relating to SARS-CoV-2, guidelines for safely conducting these procedures should consider the risk of transmitting related pathogens. Currently there is very little evidence detailing the transmission of SARS-CoV-2 associated with any specific procedures. Regarding AGPs and respiratory pathogens in general, there is still a large knowledge gap that will leave clinicians unsure of the risk to themselves when offering these procedures. This review aimed to summarize the evidence (and gaps in evidence) around AGPs and SARS-CoV-2.

Introduction

Since first being reported in December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread worldwide. The resulting coronavirus disease of 2019 (COVID-19) was declared a pandemic by the World Health Organization (WHO) in March 2020 [1]. SARS-CoV-2 is considered to primarily be spread by droplet transmission and direct contact [2,3]. Given the behaviour of similar viruses such as severe acute respiratory syndrome (SARS, also known as SARS-CoV-1), Middle East respiratory syndrome (MERS) and the influenza viruses it is very likely that it can also be spread in an airborne manner by aerosolized particles [4,5]. It is unclear how significant the roles of airborne transmission and transmission related to aerosol-generating procedures (AGPs) are in the spread of SARS-CoV-2. This is a knowledge gap that leaves clinicians unsure whether procedures are safe to undertake. Lack of clarity of risk may in turn lead to preventable infections of healthcare workers if procedures are undertaken without appropriate protection, or to worse outcomes for patients if procedures are withheld due to safety concerns. Without

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specific data relating to SARS-CoV-2, varying guidelines have been established based on general principles and research from SARS and other viruses.

It is likely that there is a hierarchy of AGPs in the sense that they each will convey a different degree of risk of infection transmission. Consequently, and in the setting of limited evidence, there is disagreement between guidelines as to which procedures should be considered AGPs and how significant the associated infection risk is. Guidelines generally consider at least intubation, pre-intubation ventilation, bronchoscopy, tracheotomy, open airway suctioning, cardiopulmonary resuscitation (CPR) and non-invasive ventilation (NIV) to be AGPs. In some instances administration of nebulized medications, use of high-flow nasal canulae (HFNC), use of oxygen masks, nasopharyngeal swabbing, and sputum induction are considered AGPs, whereas other authors have included endoscopy and transoesophageal echocardiography (TOE) [6–11]. For these procedures it is generally advised that in addition to standard precautions: a patient is isolated in a negative pressure room; procedures are performed by the most skilled operator available; healthcare workers (HCWs) should always wear gown, gloves, and an N95-level mask in the patient room; and that these procedures are only undertaken when absolutely necessary [6,12,13].

The aim of this review is to establish the current understanding of the risk of SARS-CoV-2 infection associated with AGPs. Where evidence specific to SARS-CoV-2 is absent, we aimed to determine what conclusions can be made based on data related to other viral infections and to discuss the impact of this knowledge gap and guidelines developed from it.

Methods

A review of literature was performed using PubMed, Embase, the Cochrane Library, and the WHO COVID-19 database. Searches were made for all articles up until the review date of April 1st, 2020.

Searches were made for: 'COVID-19' (and related terms) and 'infectivity', 'transmission', 'airborne' or 'aerosol'; 'aerosol generating procedures' and 'transmission' or 'infectivity'; and specific AGPs ('intubation', 'tracheostomy', 'bronchoscopy', 'airway suctioning', 'non-invasive ventilation', 'high flow nasal canulae', 'transoesophageal echocardiography', 'endoscopy' or 'nebuliser') and 'transmission' or 'infectivity'.

Abstracts were reviewed for relevance and bibliographies of relevant papers were searched for related papers which were subsequently examined. Google search engine was used to identify further literature which was not published in scientific journals and health statistics.

Results

Transmission of SARS-CoV-2

There are no reviews or trials investigating whether AGPs are associated with transmission of SARS-CoV-2. It has been established that there is rapid spread between humans in close proximity and that HCWs may be at increased risk of infection. In late February 2020 HCWs were reported to comprise only 3.8% of cases in Wuhan, but by late March the Istituto Superiore di Sanita in Italy was reporting that HCWs made up nearly 10% of Italian cases [14–16]. Although this is less than during the SARS outbreak of 2003 (21% HCWs) it is clear that HCWs are at a significant risk at least in some circumstances [17].

It is not clear to what degree HCWs are being infected despite effective droplet precautions compared with those who are infected as a result of inadequate droplet transmission personal protective equipment (PPE). Wang *et al.* suggest that the considerable number of early healthcare infections and deaths may have been due to a combination of: inadequate PPE due to lack of awareness early in the epidemic, large-scale exposure to infected patients; shortage of PPE; and inadequate infection prevention training [18].

There are case reports suggesting that airborne transmission may be occurring and it has been shown that SARS-CoV-2 can survive in aerosols for $\geq$3 h (with a similar reduction in titre as occurs with SARS-CoV-1) [2,19,20]. This does not confirm airborne transmission, but it establishes that airborne transmission is feasible and supports comparisons between SARS-CoV-2 and SARS-CoV-1 transmission routes.

Against the claim that there may be high risk of airborne transmission, Ng *et al.* reported from Singapore regarding 41 healthcare workers (HCWs) who were exposed to a SARS-CoV-2-positive patient during AGPs (including high-risk AGP procedures such as non-invasive ventilation, emergency intubation, and subsequent extubation) before the diagnosis was known [21]. Eighty-five percent of these workers wore only surgical masks and none of them developed COVID-19. Another study from Hong Kong reported on 71 staff and 49 patients who were exposed in hospital to a patient with COVID-19 before diagnosis. In this instance the patient had received 8 L/min oxygen but no other AGPs. Contacts who developed respiratory symptoms or fevers were tested for SARS-CoV-2 (52 people tested) and none was positive [22]. As further evidence is presented we will have to reassess our understanding and review guidelines. At the present time no guidelines could be established based on specific evidence of infectivity of SARS-CoV-2 during AGPs. However, there is a high likelihood that SARS-CoV-2 transmission is similar to SARS and we must presume that there is a significant risk of airborne transmission with AGPs until and unless new data demonstrate otherwise.

AGPs and viral transmission

Overview

Evidence that individual procedures may increase risk of viral transmission has predominantly arisen from the SARS outbreak of 2002–3. During that time there were reports of airborne transmission of SARS and investigation into viral transmission related to AGPs [23–25]. Subsequent investigation involving influenza virus and MERS has also occurred [5,26]. Data relating to potential AGPs are presented in Table I which describes the findings and the quality of evidence as it pertains to transmission of SARS-CoV-2. Despite these data and ongoing investigation there is still no consensus on which procedures constitute high-risk procedures for transmission of viral infections in general or in particular.

The WHO guideline on infection prevention and control of acute respiratory infections discusses the significant knowledge gap regarding AGPs and the lack of agreement as to which procedures should be included. They base their guidance on the widely referenced systematic review by Tran *et al.* which

Table I
Risk of nosocomial transmission with aerosol-generating procedures with SARS-CoV-2

Procedure	Studies	Findings	Quality	References
Intubation	Eight observational studies in three countries investigating risk of SARS transmission to exposed HCWs.	Significant increase in risk of transmission seen in six studies. Combined odds ratio of 6.6 reported in meta-analysis.	Low — Conclusions extrapolated from SARS — Small retrospective studies only — Consistent findings shown	[27—35]
Tracheotomy, CPR and manual ventilation	Five studies in two countries investigating risk of SARS transmission to exposed HCWs.	No clear increase in infection risk. Only one study analysed tracheotomy and found a significantly increased transmission risk but this was not seen in multivariate analysis. Three out of four studies suggested an increased infection risk associated with resuscitation (chest compression or pre-intubation ventilation) but could not separate effect of these procedures from intubation. No significant effect was seen associated with defibrillation.	Very low — Conclusions extrapolated from SARS — Small retrospective studies only — Inconsistent findings — Confounding variables not accounted for.	[28—30,32,36]
Bronchoscopy and airway suctioning	Two cohort studies in one country investigating risk of SARS transmission to exposed HCWs. One study tested for presence of influenza RNA in aerosols from patient rooms during AGPs.	No clear increase in risk. Neither SARS study showed significant increased risk of infection with bronchoscopy or any effect of airway suctioning. Bronchoscopy was the only AGP associated with increased probability of influenza detection in aerosols.	Very low — Conclusions extrapolated from SARS and influenza — Uncertain significance of indirect finding of RNA detection — Very small studies only — Inconsistent and imprecise results	[28,29,37]
Non-invasive ventilation (NIV)	Four observational studies from two countries investigating risk of SARS transmission. One further study examining dispersal of air during NIV and another measuring aerosols/droplets produced.	No clear increase in risk has been demonstrated. Three studies showed a trend towards increased risk of SARS transmission, two results were statistically significant (although not upheld in multivariate analysis). The fourth study showed no infections in 105 HCWs exposed to NIV although they did not assess risk in non-exposed workers. Air dispersal was detected to ∼1 m but no significant increase in aerosol production was shown.	Very low — Conclusions extrapolated from SARS — Small studies only — Inconsistent results — Uncertain significance of indirect finding such as air dispersal and aerosol production in healthy volunteers	[28,38,39,30,40,31]
High-flow nasal canulae (HFNC) and oxygen masks	Two observational studies from one country investigating risk of SARS transmission looked at manipulation	Both studies showed a small trend towards increased risk with manipulation of oxygen mask (the	Very low — Conclusions extrapolated from SARS and bacterial infections	[28,29,41]

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Table I (*continued*)

Procedure	Studies	Findings	Quality	References
	of oxygen masks (one of which also looked at HFNC). One randomized control trial compared effect of HFNC vs oxygen masks on bacterial cultures in rooms of patients with bacterial pneumonia	small study showed a significant effect). HFNC was not shown to have a significant effect. No difference in bacterial count between HFNC and oxygen masks was demonstrated.	— Small studies only — Inconsistent results — Confounding variables not accounted for — Uncertain significance of indirect findings regarding bacterial cultures	
Nebulizer treatment	Three observational studies from two countries investigating risk of SARS transmission. An additional study measured aerosol dispersal during nebulizer use.	Two studies showed a correlation but both were small and neither showed a significant increase in infection risk. Significantly increased numbers of aerosols were detected at 1 m distance from patients during nebulizer use.	Very low — Conclusions extrapolated from SARS — Very small studies — Inconsistent results and wide confidence intervals — Finding of aerosol production during nebulizer use is unlikely to be clinically important	[28,29,42,43]
Nasopharyngeal swabbing and collection of sputum	One observational study investigating risk of SARS transmission assessed collection of sputum.	No significant effect on infection risk was seen (four infected out of 42 exposed).	Very low — Conclusions extrapolated from SARS — Very small study — Wide confidence interval — No evidence regarding nasopharyngeal swabbing	[28]
Endoscopy and transoesophageal echocardiography	One prospective study investigating bacterial growth from facemasks used during endoscopies.	Significantly increased colony-forming units detected post endoscopy compared to controls.	Very low — Conclusion extrapolated from study of bacteria — Indirect study with regard to aerosol transmission	[44]

SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; HCWs, healthcare workers; CPR, cardiopulmonary resuscitation; AGP, aerosol-generating procedure.

identifies tracheal intubation as the only procedure which is consistently associated with SARS transmission [27]. In accordance with this meta-analysis, the WHO states that NIV, tracheotomy and manual ventilation before intubation are associated with infection transmission in a few small studies, and the evidence was deemed to be very low quality by the reviewers. They state that no other procedures have been found to be significantly associated with infection transmission – investigated procedures were suction of body fluids, endotracheal aspiration and other intubation associated procedures, bronchoscopy, nebulized medication administration, use of HFNC, use of and manipulation of oxygen mask or bilevel positive airway pressure mask, defibrillation, chest compressions, insertion of nasogastric tube, and collection of sputum.

The US Centers for Disease Control and Prevention provide a list of procedures that they report are often considered AGPs: open suctioning of airways, sputum induction, CPR, endotracheal intubation and extubation, NIV, bronchoscopy and manual ventilation. They state that it is uncertain whether nebulizer administration and high-flow oxygen delivery produce infectious aerosols. The European Centre for Disease Prevention and Control guidance from March 2020 lists tracheal intubation, bronchial suctioning, and sputum induction as examples of AGPs and emphasizes that nasopharyngeal swabbing should also be considered an AGP [9].

Intubation, tracheotomy, CPR, and manual ventilation

Endotracheal intubation of SARS-infected patients has been consistently associated with viral transmission to HCWs [45]. Eight observational studies investigated this issue and Tran *et al.* and demonstrated an odds ratio (OR) of 6.6 (95% confidence interval (95% CI): 2.3–18.9) from the four cohort studies and an OR of 6.6 (95% CI: 4.1–10.6) from the four case–control studies [27].

Current evidence shows an increased risk of transmission during resuscitation but it is difficult to separate the effects of individual procedures in the resuscitation process or to separate pre-intubation ventilation from intubation itself [24,46]. Mechanical ventilation and CPR have been investigated in some studies where they have not been shown to be associated with SARS (or other acute respiratory infection) transmission [28,29]. In the 2009 study by Liu *et al.* chest compressions were associated with infection risk but HCWs involved with chest compressions were more likely to be present at time of intubation and the authors found that these variables could not be distinguished from each other [46].

Due to the lack of strong evidence against any infection risk, and due to likelihood of associated intubation with resuscitation, measures such as CPR, manual ventilation, and tracheotomy are reasonably considered to be high-risk for infection transmission.

Bronchoscopy and airway suctioning

Bronchoscopy was not associated with infection transmission in the two studies published during the SARS outbreak. In one study, 10 HCWs were exposed to bronchoscopy and none developed the infection; in the other, two HCWs were exposed and one developed SARS [28,29]. Subsequent investigation based on influenza A H1N1 suggested an increased detection of viral aerosols following bronchoscopy and airway suctioning [37]. Bacteria have been detected in ambient air following bronchoscopic procedures but risk to HCWs has not been studied further [47].

Open suctioning of intubated patients' airways involves disconnecting the tracheal tube from the ventilator, and this, or the suction itself, may lead to dispersal of aerosols from within the airway. Increased number of airborne particles near patients has been detected in association with airway suctioning but increased infection risk has not been demonstrated [48].

Non-invasive ventilation

There is considerable disagreement about the risk of aerosolization and transmission of viruses due to NIV. Exhaled virus or aerosols have not been detected during its use and the evidence suggesting that NIV increases risk of acute respiratory infections is not strong [49,50]. In a widely referenced study, Hui *et al.* demonstrated that air originating in a patient's airways may be spread within a radius of $\sim$1 m during NIV use [38]. Subsequent studies show that whereas incorrect fitting of masks considerably increases the spread of exhaled air, in general there is not widespread dispersion of exhaled air [42,51]. Furthermore there is little evidence of droplet or aerosol particles even within the 1 m range [39]. There are no studies to show that air or aerosols distributed by NIV masks contain viral particles or fluid from the respiratory tract.

NIV has not been clearly shown to increase risk of infection with SARS or other viral diseases; however, there are studies and case reports describing an association [27,52].

Raboud *et al.* surveyed 624 HCWs exposed to 45 confirmed SARS patients who were all intubated during the Toronto SARS outbreak in 2003 [28]. Twenty-six HCWs contracted SARS and 22 of these were attributed to a single patient. SARS developed in 38% of HCWs exposed to NIV compared with 17% of those who did not, which was a statistically significant association; however, this association was not upheld by generalized estimating equation logistic regression or multivariate analysis. Of note, HCW presence during electrocardiogram recording was considered a stronger risk factor than during NIV – this suggests that variables other than aerosol generation played a considerable role in HCW risk.

Loeb *et al.* and Yu *et al.* also reported an association between NIV and SARS transmission but found a stronger association related to oxygen masks [29,30]. It is hypothesized that NIV may provide a protective benefit by limiting dispersal of droplets as patients cough [53]. Whereas NIV failure rates are higher in de-novo ARDS than in exacerbations of chronic disease, the prevention of a patient from requiring intubation may reduce risk of disease transmission. Cheung *et al.* reported on 105 HCWs exposed to 20 patients undergoing NIV in 2003 in Hong Kong [40]. None of their HCWs subsequently contracted SARS. They did not comment on what precautions were taken and what PPE was worn, leaving open the question whether they may have enforced stricter infection prevention measures than other centres.

HFNC and oxygen masks

In the one review from the SARS outbreak which documented use of HFNC it was not shown to have an effect on risk of infection transmission. Manipulation of oxygen masks was significant in one of only two studies in which very small sample sizes were used and confidence intervals were large [28,29].

In simulated and experimental studies, HFNC and oxygen masks have been shown to disperse droplets and inhaled aerosols within a radius up to 0.5–0.6 m. This is less than with NIV and continuous positive airway pressure (CPAP) masks, was noted to be flow rate dependent, and was maximized by incorrectly fitting masks [51,54,55]. Loh *et al.* recently demonstrated that use of HFNC may increase distance of droplet dispersal with coughing from an average of 2.48–2.91 m in a study with five volunteers [56]. Compared with conventional oxygen masks, HFNC use was not associated with increased dispersal of bacterial particles in one study [41]. Specific studies with viruses have not been conducted. It remains unclear whether HFNC should be considered an AGP based on its production or spread of droplets, and there is insufficient evidence to confirm an associated infection risk.

Some association has been demonstrated between manipulation of oxygen masks and infection transmission, but neither were considered significant findings. Subsequent studies have shown no association [27,50,57].

Nebulizer treatment

Risk of transmission of SARS with nebulizer treatment received attention after a Hong Kong hospital reported widespread transmission of SARS after a patient had been treated with regular salbutamol nebulizers on the ward for seven days [58]. Beyond the review by Tran *et al.* there has been little subsequent research into the risk of transmission during nebulizer treatment [27]. Tran *et al.* found two studies showing that nebulizer use was associated with transmission of SARS, whereas one other did not. Their meta-analysis showed a wide confidence interval and no statistically significant effect. It is noted by Simonds *et al.* that there is considerable dispersal of aerosolized particles from a nebulizer, but there is no research investigating whether particles originate in the patient or the nebulizer itself or whether viruses can be isolated from these particles [42].

Nasopharyngeal swabbing and collection of sputum

Risk of contracting SARS after sputum induction was considered by one study with 42 HCWs involved with sputum collection. It was found that four of these HCWs developed SARS, which amounted to a small but not significant correlation [28]. Further research is clearly required to establish whether there is any risk of airborne transmission; however, the increased risk of droplet transmission related to coughing within close proximity is well understood and is likely to contribute to increased risk of infection if PPE is not adequate.

Endoscopy and transoesophageal echocardiography

There is no evidence that endoscopy or TOE generate aerosols or convey an increased risk of transmission of viruses. It has only been shown that there is bacterial exposure to proceduralists during endoscopy procedures by culturing swabs taken from endoscopists' face shields after their procedures [44]. It has been suggested that endoscopic procedures for patients that are intermediate to high risk of being infected with SARS-CoV-2 should be treated with airborne precautions due to risk of viral transmission, but there is no further evidence to support this [10].

It has also been claimed that TOE should be considered an AGP but there have been no specific studies on TOE to establish any increased risk of viral transmission. Driggen *et al.* suggest that consideration for increased precautions should be given to procedures associated with increased risk of patient deterioration, as resuscitation is associated with increased disease transmission [11]. As discussed previously, this may be reasonable but it should not be taken from this argument that TOE is an AGP or that it directly increases HCW infection risk.

Discussion

Current evidence

There is almost no evidence pertaining directly to the infectivity of SARS-CoV-2 during AGPs. Guidelines have been established mostly based on evidence related to SARS. Research on SARS and H1N1 influenza A has established endotracheal intubation to be associated with infection transmission despite droplet infection precautions. Evidence does not confirm an association between other AGPs and infection risk when appropriate droplet PPE and precautions are used.

Aerosol-generating procedures such as CPR, pre-intubation ventilation, tracheostomy, and bronchoscopy do not currently have strong evidence to support an association with increased transmission but are generally considered high-risk procedures. These procedures are likely to increase transmission either directly or due to their close association with intubation. Other factors, such as increased infectivity in more severe illness and less stringent use of PPE in acute emergencies, may also contribute. Whereas other AGPs are often undertaken in emergencies, bronchoscopy in general may be undertaken in a routine manner – given the possible increased risk of transmission and the lack of specific data on SARS-CoV-2, it is reasonable that bronchoscopy be avoided unless absolutely necessary.

Procedures such as NIV, HFNC, and administration of medications by nebulizers have not been consistently associated with infection transmission. It is reasonable to limit any unnecessary usage but it is not clear that they should be withheld in patients who are likely to benefit from them. There is not enough evidence to suggest that any other procedures cause a risk of infection transmission, and a definitive list of which procedures carry risk, and should be considered AGPs, has not be established. Further research is required to establish what transmission risk these procedures do carry and how clinicians can appropriately protect themselves. Guidelines should reflect the conclusions that can be made and the lack of evidence in other areas.

Guideline development and social factors

There are substantial gaps in evidence for the SARS-CoV-2 pandemic around transmission routes, risk to HCWs, and safety of AGPs. Indeed there is a paucity of evidence with regard to infection risk associated with AGPs in general. These evidence gaps have not only produced a vacuum in knowledge of best practice, they have quickly fostered cultures of uncertainty among HCWs across many contexts. This has resulted in a range of consequences including likely increases in infective risks (through variation in practices and potentially unnecessary depletion of finite resources) and lack of capacity to provide care when needed (due to fear of contagion).

In many respects, like other facets of the COVID-19 pandemic, the contagion is not only viral, but is behavioural. In this context, it is driven by unprecedented levels of professional uncertainty which offer the very real threat of widespread sub-optimal practices. As shown in other contexts, such as Ebola, MERS, or SARS, the precarity that is experienced by HCWs in the midst of such an evidence vacuum produces, among other problems, highly localized practices (i.e. that are too stringent, or indeed, too lax), workplace absenteeism, and even withdrawal from providing treatment in frontline settings [59–62]. In this sense, gathering best evidence around issues such as AGPs, which are currently being heavily debated within the context of COVID-19, provides a means of both mitigating uncertainty and acknowledging uncertainty as an important challenge for HCWs during this pandemic.

When considering the threats to HCWs it is also worth emphasizing that the task ahead is not simply a matter of producing evidence across all relevant procedures that may harbour risks of transmission, but promoting understanding of the impact of some level of uncertainty, and ensuring that we are able to offset the potential for the parallel health service 'contagion' of anxiety around transmission risk through consistent messaging, consistent policies and practices, well-resourced PPE, and streamlined national and international guidelines.

Conclusion

Aerosol-generating procedures are an important consideration for HCWs during the COVID-19 pandemic. There is no evidence demonstrating an increased infection risk related to AGPs in SARS-CoV-2, but in related viruses a risk has been shown associated specifically with intubation of infected patients, and it is possible that other AGPs convey a risk as well. There is a significant knowledge gap in this area and the risk that HCWs face has not been established. Guidelines are necessary to ensure that HCWs are aware of this fact and that their practice is consistent, appropriate, and safe.

Healthcare worker risk may be increased further by clinical practice guidelines themselves which, written in the context of an evidence gap and of high professional anxiety, may cause wastage of protective equipment and resources, and prevent useful clinical interventions or otherwise influence individual patient treatment. We must mitigate uncertainty and anxiety not only by research to provide further evidence on which to guide practice, but by providing consistent and transparent guidelines and advice, and ensuring that HCWs have appropriate PPE readily available.

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