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EVIDENCE SEARCH REPORT

RESEARCH QUESTION: What is the degree of COVID-19 transmission through the administration of nebulizer medication either in clinical practice or in animal experiments?	**UNIQUE IDENTIFIER:** EOC040101-01 ESR

RESOURCES USED:

- CINAHL
- CDC
- Cochrane Library
- COVID-1
- Google
- Google Scholar
- Health Canada
- LitCovid
- Medline
- medRxiv
- PubMed
- Reference mining
- WHO Global Research on COVID-19

LIMITS/EXCLUSIONS/INCLUSIONS: English	**REFERENCE INTERVIEW COMPLETED:**
DATE: April 1, 2020	
LIBRARIAN: Michelle Dalidowicz & Catherine Young	**REQUESTOR:** Dr. Gary Groot, Dr. Mark Fenton

TEAM: EOC

CITE AS: Dalidowicz, M; Young, C. What is the degree of COVID-19 transmission through the administration of nebulizer medication either in clinical practice or in animal experiments? 2020 Apr 1; Document no.: EOC040101-01 ESR. In: COVID-19 Rapid Evidence Reviews [Internet]. SK: SK COVID Evidence Support Team, c2020. 12 p. (CEST evidence search report)

LIBRARIAN NOTES/COMMENTS

Hi Gary

Please find the results below. We expanded the search to include SARS as requested.

Thanks,
Michelle & Catherine

SEARCH RESULTS

To obtain the full-text articles or to request offsite access, email library@saskhealthauthority.ca.

SUMMARIES, GUIDELINES & OTHER RESOURCES

Guidance

MAJOR BODIES

1. **Modes of transmission of virus causing COVID-19: implications for IPC precaution recommendations**. World Health Organization.
   https://www.who.int/news-room/commentaries/detail/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations
   - "In the context of COVID-19, airborne transmission may be possible in specific circumstances and settings in which procedures or support treatments that generate aerosols are performed; i.e., endotracheal intubation, bronchoscopy, open suctioning, administration of nebulized treatment, manual ventilation before intubation, turning the patient to the prone position, disconnecting the patient from the ventilator, non-invasive positive-pressure ventilation, tracheostomy, and cardiopulmonary resuscitation."

2. World federation of anaethesiologists. **Coronavirus - guidance for anaesthesia and perioperative care providers**
   https://www.wfsahq.org/resources/coronavirus
   - aerosol generating procedures include intubation, extubation, bronchoscopy, airway suction, high frequency oscillatory ventilation, tracheostomy, chest physiotherapy, nebulizer treatment. These procedures should be performed in the COVID-19 patient only when the benefits outweigh the risks, and when adequate PPE and staff preparation is available.

3. [for SARS] Centre for Disease Control and Prevention (CDC). **Infection Control in Healthcare, Home, and Community Settings Public Health Guidance for Community-Level Preparedness and Response to Severe Acute Respiratory Syndrome (SARS).**
   - "Because aerosol-generating procedures may pose a greater risk of SARS-CoV transmission, additional precautions are recommended for healthcare workers who perform or assist with these procedures. Procedures that stimulate coughing and promote the generation of aerosols include aerosolized or nebulized medication administration, diagnostic sputum induction, bronchoscopy, airway suctioning, endotracheal intubation, positive pressure ventilation via face mask (e.g., BiPAP, CPAP), and high-frequency oscillatory ventilation."

4. [for SARS] **IPAC (Infection Prevention and Control Canada)**
   https://ipac-canada.org/coronavirus-resources.php
   - Aerosolizing procedures in hospitals (such as nebulization), and other events that promote aerosolization of infectious respiratory droplets or other potentially infectious materials (such as faeces or urine) in hospitals or other settings, may amplify transmission. [in relation to SARS]

PROVINCES/STATES

1. BC Centre for Disease Control. **Interim Guidance: Public Health Management of cases and contacts associated with novel coronavirus (COVID-19) in the community.**

http://www.bccdc.ca/resource-gallery/Documents/Guidelines%20and%20Forms/Guidelines%20and%20Manuals/Epid/CD%20Manual/Chapter%201%20-%20CDC/2019-nCoV-Interim_Guidelines.pdf

- "If aerosol-generating medical procedures are necessary (e.g., case is receiving nebulized therapy) the use of Additional Precautions, including using a fit-tested N95 respirator and eye protection, is recommended." P.13

2. Nova Scotia Health Authority. **Coronavirus Disease. Memo: Nebulized medications.** https://www.cdha.nshealth.ca/system/files/sites/documents/memo-nebulized-meds-covid-march-19-2020.pdf

3. Alberta Health Services. **Recommendations for Antimicrobial Management of Adult Hospitalized Patients with COVID-19.** https://www.albertahealthservices.ca/assets/info/ppih/if-ppih-covid-19-recommendations.pdf
    - Avoid nebulized medications and do not do bronchoscopy for obtaining specimens alone (ET aspirate preferred) to reduce aerosolization risk.

4. Ontario Ministry of Health**. Joint Statement: COVID-19 and Health and Safety Measures, including Personal Protective Equipment.** http://www.health.gov.on.ca/en/pro/programs/publichealth/coronavirus/2019_covid_joint_statement.aspx
    - AGMPs include but are not limited to; Intubation and related procedures (e.g. manual ventilation, open endotracheal suctioning), cardio pulmonary resuscitation, bronchoscopy, sputum induction, non-invasive ventilation (i.e. BiPAP), open respiratory/airway suctioning, high frequency oscillatory ventilation, tracheostomy care, nebulized therapy/aerosolized medication administration, high flow heated oxygen therapy devices (e.g. ARVO, optiflow) and autopsy.

5. **Covid-19 guidance for infection prevention and control in healthcare settings.** Department of Health and Social Care (DHSC), Public Health Wales (PHW), Public Health Agency (PHA) Northern Ireland, Health Protection Scotland (HPS) and Public Health England as official guidance. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/876577/Infection_prevention_and_control_guidance_for_pandemic_coronavirus.pdf
    - "Certain other procedures/equipment may generate an aerosol from material other than patient secretions but are not considered to represent a significant infectious risk. Procedures in this category include: ● administration of pressurised humidified oxygen; ● administration of medication via nebulisation.
    - During nebulisation, the aerosol derives from a non-patient source (the fluid in the nebuliser chamber) and does not carry patient-derived viral particles. If a particle in the aerosol coalesces with a contaminated mucous membrane, it will cease to be airborne and therefore will not be part of an aerosol. Staff should use appropriate hand hygiene when helping patients to remove nebulisers and oxygen masks."

6. **Interim Statement on Infection Prevention and Control for the Administration of Nebulized Medication to Patients with Suspected or Confirmed COVID-19.** Minnesota Department of Health. https://www.health.state.mn.us/diseases/coronavirus/hcp/aerosol.pdf

7. [for SARS] **Infectious Diseases Protocol. Disease Specific Chapters. SARS.** Ontario Ministry of Health and Long-term care.
   http://www.health.gov.on.ca/en/pro/programs/publichealth/oph_standards/docs/sars_chapter.pdf
   - "During the 2003 outbreak, health workers were at great risk of disease acquisition, especially before the diagnosis of SARS and when involved in aerosol-generating procedures such as intubations or nebulization.1 In 2003, health care workers served as an entry point of the disease into the community in North America." P.4

Google Scholar

1. Covid-19: a puzzle with many missing pieces https://www.bmj.com/content/368/bmj.m627/rr-18

2. Jones RM, Brosseau LM. Aerosol transmission of infectious disease. Journal of occupational and environmental medicine. 2015 May 1;57(5):501-8.
   https://journals.lww.com/joem/Fulltext/2015/05000/Aerosol_Transmission_of_Infectious_Disease.4.aspx

3. Todd MC, Belteton MV. Factors Involved in Aerosol Transmission of Infection and Control of Ventilation in Healthcare. InNoninvasive Ventilation in High-Risk Infections and Mass Casualty Events 2014 (pp. 269-277). Springer, Vienna.
   https://link.springer.com/chapter/10.1007/978-3-7091-1496-4_30

Books

1. Low DE. SARS: LESSONS FROM TORONTO. In: Institute of Medicine (US) Forum on Microbial Threats; Knobler S, Mahmoud A, Lemon S, et al., editors. Learning from SARS: Preparing for the Next Disease Outbreak: Workshop Summary. Washington (DC): National Academies Press (US); 2004.
   Quote from full-text: "Nosocomial transmission in the hospital began when case A presented to the emergency department on March 7 with severe respiratory symptoms. He was placed in a general observation area of the emergency department and received nebulized salbutamol. During this time, SARS was transmitted to two other patients in the emergency department (cases B and C)."
   ACCESS URL: https://www.ncbi.nlm.nih.gov/books/NBK92467/

ARTICLES FROM THE LIBRARY DATABASES

Note: References are sorted by year descending (newest to oldest)

1. **Respiratory care committee of Chinese Thoracic S. [Expert consensus on preventing nosocomial transmission during respiratory care for critically ill patients infected by 2019 novel coronavirus pneumonia]. Chung Hua Chieh Ho Ho Hu Hsi Tsa Chih. 2020;17(0):E020. DOI: https://dx.doi.org/10.3760/cma.j.issn.1001-0939.2020.0020**
   Definite evidence has shown that the novel coronavirus (COVID-19) could be transmitted from person to person, so far more than 1,700 bedside clinicians have been infected. A lot of respiratory treatments for critically ill patients are deemed as high-risk factors for nosocomial transmission, such as intubation, manual ventilation by resuscitator, noninvasive ventilation, high-flow nasal cannula, bronchoscopy examination, suction and patient transportation, etc, due to its high possibility to cause or worsen the spread of the virus. As such, we developed this consensus recommendations on all those high-risk treatments, based on the current evidence as well as the resource limitation in some areas, with the aim to reduce the nosocomial transmission and optimize the treatment for the COVID-19 pneumonia

patients. Those recommendations include: (1) Standard prevention and protection, and patient isolation; (2) Patient wearing mask during HFNC treatment; (3) Using dual limb ventilator with filters placed at the ventilator outlets, or using heat-moisture exchanger (HME) instead of heated humidification in single limb ventilator with HME placed between exhalation port and mask; avoid using mask with exhalation port on the mask; (4) Placing filter between resuscitator and mask or artificial airway; (5) For spontaneous breathing patients, placing mask for patients during bronchoscopy examination; for patients receiving noninvasive ventilation, using the special mask with bronchoscopy port to perform bronchoscopy; (6) Using sedation and paralytics during intubation, cuff pressure should be maintained between 25-30 cmH(2)O; (7) In-line suction catheter is recommended and it can be used for one week; (8) Dual-limb heated wire circuits are recommended and only changed with visible soiled; (9. For patients who need breathing support during transportation, placing an HME between ventilator and patient; (10) PSV is recommended for implementing spontaneous breathing trial (SBT), avoid using T-piece to do SBT. When tracheotomy patients are weaned from ventilator, HME should be used, avoid using T-piece or tracheostomy mask. (11) Avoid unnecessary bronchial hygiene therapy; (12) For patients who need aerosol therapy, dry powder inhaler metered dose inhaler with spacer is recommended for spontaneous breathing patients; while vibrating mesh nebulizer is recommended for ventilated patients and additional filter is recommended to be placed at the expiratory port of ventilation during nebulization.
ACCESS ARTICLE URL:
http://rs.yiigle.com/yufabiao/1182334.htm

2. **Nam HS, Park JW, Ki M, et al. High fatality rates and associated factors in two hospital outbreaks of MERS in Daejeon, the Republic of Korea. Int J Infect Dis. 2017;58:37-42. DOI: https://dx.doi.org/10.1016/j.ijid.2017.02.008**
OBJECTIVES: To explore the epidemiological and clinical factors predictive of the case fatality rate (CFR) of Middle East respiratory syndrome-coronavirus (MERS-CoV) infection in an outbreak in Daejeon, the Republic of Korea.
METHODS: We reviewed the outbreak investigation reports and medical records of 1 index case and 25 additional MERS cases in hospitals A (14 cases) and B (11 cases), and conducted an in-depth interview with the index case.
RESULTS: The CFR in hospital B was higher than that in hospital A (63.6% vs. 28.6%, respectively). Higher MERS-CoV exposure conditions were also found in hospital B, including aggravated pneumonia in the index case and nebulizer use in a six-bed admission room. The host factors associated with high CFR were pre-existing pneumonia, smoking history, an incubation period of less than 5 days, leukocytosis, abnormal renal function at diagnosis, and respiratory symptoms such as sputum and dyspnea.
CONCLUSIONS: The conditions surrounding MERS-CoV exposure and the underlying poor pulmonary function due to a smoking history or pre-existing pneumonia may explain the high CFR in hospital B. The clinical features described above may enable prediction of the prognosis of MERS cases.

3. **Wishaupt JO, van der Ploeg T, de Groot R, et al. Single- and multiple viral respiratory infections in children: disease and management cannot be related to a specific pathogen. BMC Infect Dis. 2017;17:1-11. DOI: 10.1186/s12879-016-2118-6**
Background: The number of viral pathogens associated with pediatric acute respiratory tract infection (ARI) has grown since the introduction of reverse transcription real-time polymerase chain reaction (RT-PCR) assays. Multiple viruses are detected during a single ARI episode in approximately a quarter of all cases. The clinical relevance of these multiple detections is unclear, as is the role of the individual virus. We therefore investigated the correlation between clinical data and RT-PCR results in children with single- and multiple viral ARI.Methods: Data from children with ARI were prospectively collected during two winter seasons. RT-PCR testing for 15 viruses was performed in 560 ARI episodes. In the patients

with a single-viral etiology, clinical data, laboratory findings, patient management- and outcome data were compared between the different viruses. With this information, we compared data from children of whom RT-PCR data were negative, with children with single- and multiple viral positive results.Results: The viral detection rate was 457/560 (81.6%) of which 331/560 (59.1%) were single infections and 126/560 (22.5%) were multiple infections. In single viral infections, some statistically significant differences in demographics, clinical findings, disease severity and outcome were found between children with different viral etiologies. However, no clinically recognizable pattern was established to be virus-specific. In a multivariate analysis, the only variables that were correlated with longer hospital stay were the use of oxygen and nebulizer therapy, irrespective of the viral pathogen. Children with RT-PCR positive test results had a significant higher disease severity, fever, length of hospital stay, days of extra oxygen supply, and days of antibiotic treatment than children with a negative RT-PCR test result. For children with single- versus children with multiple positive RT-PCR test results, these differences were not significant.Conclusions: Disease (severity), management and outcome in pediatric ARI are not associated with a specific virus. Single- and multiple viral ARI do not significantly differ with regard to clinical outcome and patient management. For general pediatrics, RT-PCR assays should be restricted to pathogens for which therapy is available or otherwise may have clinical consequences. Further research with an extended panel of RT-PCR assays and a larger number of inclusions is necessary to further validate our findings.
ACCESS ARTICLE URL:
https://bmcinfectdis.biomedcentral.com/track/pdf/10.1186/s12879-016-2118-6

4. **Park SH, Kim YS, Jung Y, et al. Outbreaks of Middle East Respiratory Syndrome in Two Hospitals Initiated by a Single Patient in Daejeon, South Korea. Infect. 2016;48(2):99-107. DOI: https://dx.doi.org/10.3947/ic.2016.48.2.99**
BACKGROUND: A Middle East Respiratory Syndrome coronavirus (MERS-CoV) outbreak in South Korea in 2015 started by a single imported case and was amplified by intra- and inter-hospital transmission. We describe two hospital outbreaks of MERS-CoV infection in Daejeon caused by a single patient who was infected by the first Korean case of MERS.
MATERIALS AND METHODS: Demographic and clinical information involving MERS cases in the Daejeon cluster were retrospectively collected and potential contacts and exposures were assessed. The incubation periods and serial intervals were estimated. Viral RNAs were extracted from respiratory tract samples obtained from the index case, four secondary cases and one tertiary case from each hospital. The partial S2 domain of the MERS-CoV spike was sequenced.
RESULTS: In Daejeon, a MERS patient (the index case) was hospitalized at Hospital A in the first week of illness and was transferred to Hospital B because of pneumonia progression in the second week of illness, where he received a bronchoscopic examination and nebulizer therapy. A total of 23 secondary cases (10 in Hospital A and 13 in Hospital B) were detected among patients and caregivers who stayed on the same ward with the index case. There were no secondary cases among healthcare workers. Among close hospital contacts, the secondary attack rate was 15.8% (12/76) in Hospital A and 14.3% (10/70) in Hospital B. However, considering the exposure duration, the incidence rate was higher in Hospital B (7.7/100 exposure-days) than Hospital A (3.4/100 exposure-days). In Hospital B, the median incubation period was shorter (4.6 days vs. 10.8 days), the median time to pneumonia development was faster (3 days vs. 6 days) and mortality was higher (70% vs. 30.8%) than in Hospital A. MERS-CoV isolates from 11 cases formed a single monophyletic clade, with the closest similarity to strains from Riyadh.
CONCLUSION: Exposure to the MERS case in the late stage (2nd week) of diseases appeared to increase the risk of transmission and was associated with shorter incubation periods and rapid disease progression among those infected. Early detection and isolation of cases is critical in preventing the spread of MERS in the hospital and decreasing the disease severity among those infected.
ACCESS ARTICLE URL:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4945733/pdf/ic-48-99.pdf

5. **Raboud J, Shigayeva A, McGeer A, et al. Risk factors for SARS transmission from patients requiring intubation: a multicentre investigation in Toronto, Canada. PLoS ONE. 2010;5(5):e10717. DOI: 10.1371/journal.pone.0010717**
BACKGROUND: In the 2003 Toronto SARS outbreak, SARS-CoV was transmitted in hospitals despite adherence to infection control procedures. Considerable controversy resulted regarding which procedures and behaviours were associated with the greatest risk of SARS-CoV transmission. METHODS: A retrospective cohort study was conducted to identify risk factors for transmission of SARS-CoV during intubation from laboratory confirmed SARS patients to HCWs involved in their care. All SARS patients requiring intubation during the Toronto outbreak were identified. All HCWs who provided care to intubated SARS patients during treatment or transportation and who entered a patient room or had direct patient contact from 24 hours before to 4 hours after intubation were eligible for this study. Data was collected on patients by chart review and on HCWs by interviewer-administered questionnaire. Generalized estimating equation (GEE) logistic regression models and classification and regression trees (CART) were used to identify risk factors for SARS transmission. RESULTS: 45 laboratory-confirmed intubated SARS patients were identified. Of the 697 HCWs involved in their care, 624 (90%) participated in the study. SARS-CoV was transmitted to 26 HCWs from 7 patients; 21 HCWs were infected by 3 patients. In multivariate GEE logistic regression models, presence in the room during fiberoptic intubation (OR = 2.79, p = .004) or ECG (OR = 3.52, p = .002), unprotected eye contact with secretions (OR = 7.34, p = .001), patient APACHE II score > or = 20 (OR = 17.05, p = .009) and patient Pa0(2)/Fi0(2) ratio < or = 59 (OR = 8.65, p = .001) were associated with increased risk of transmission of SARS-CoV. In CART analyses, the four covariates which explained the greatest amount of variation in SARS-CoV transmission were covariates representing individual patients. CONCLUSION: Close contact with the airway of severely ill patients and failure of infection control practices to prevent exposure to respiratory secretions were associated with transmission of SARS-CoV. Rates of transmission of SARS-CoV varied widely among patients.

6. **Simonds A, Hanak A, Chatwin M, et al. Evaluation of droplet dispersion during non-invasive ventilation, oxygen therapy, nebuliser treatment and chest physiotherapy in clinical practice: implications for management of pandemic influenza and other airborne infections. Health Technology Assessment. 2010;14(55):131-72. DOI: 10.3310/hta14460-02**
BACKGROUND: Influenza viruses are thought to be spread by droplets, but the role of aerosol dissemination is unclear and has not been assessed by previous studies. Oxygen therapy, nebulised medication and ventilatory support are treatments used in clinical practice to treat influenzal infection are thought to generate droplets or aerosols. OBJECTIVES: Evaluation of the characteristics of droplet/aerosol dispersion around delivery systems during non-invasive ventilation (NIV), oxygen therapy, nebuliser treatment and chest physiotherapy by measuring droplet size, geographical distribution of droplets, decay in droplets over time after the interventions were discontinued. METHODS: Three groups were studied: (1) normal controls, (2) subjects with coryzal symptoms and (3) adult patients with chronic lung disease who were admitted to hospital with an infective exacerbation. Each group received oxygen therapy, NIV using a vented mask system and a modified circuit with non-vented mask and exhalation filter, and nebulised saline. The patient group had a period of standardised chest physiotherapy treatment. Droplet counts in mean diameter size ranges from 0.3 to > 10 um were measured with an counter placed adjacent to the face and at a 1-m distance from the subject/patient, at the height of the nose/mouth of an average health-care worker. RESULTS: NIV using a vented mask produced droplets in the large size range (> 10 um) in patients (p = 0.042) and coryzal subjects (p = 0.044) compared with baseline values, but not in normal controls (p = 0.379), but this increase in large droplets was not seen using the NIV circuit modification. Chest physiotherapy produced droplets

predominantly of > 10 um (p = 0.003), which, as with NIV droplet count in the patients, had fallen significantly by 1 m. Oxygen therapy did not increase droplet count in any size range. Nebulised saline delivered droplets in the small- and medium-size aerosol/droplet range, but did not increase large-size droplet count. CONCLUSIONS: NIV and chest physiotherapy are droplet (not aerosol)-generating procedures, producing droplets of > 10 um in size. Due to their large mass, most fall out on to local surfaces within 1 m. The only device producing an aerosol was the nebuliser and the output profile is consistent with nebuliser characteristics rather than dissemination of large droplets from patients. These findings suggest that health-care workers providing NIV and chest physiotherapy, working within 1 m of an infected patient should have a higher level of respiratory protection, but that infection control measures designed to limit aerosol spread may have less relevance for these procedures. These results may have infection control implications for other airborne infections, such as severe acute respiratory syndrome and tuberculosis, as well as for pandemic influenza infection.
ACCESS ARTICLE URL:
https://www.journalslibrary.nihr.ac.uk/hta/hta14460-02/#/abstract

7. **Chan-Yeung M. Severe acute respiratory syndrome (SARS) and healthcare workers. Int J Occup Environ Health. 2004;10(4):421-7.**
The recent outbreak of severe acute respiratory (SARS) was spread by international air travel, a direct result of globalization. The disease is caused by a novel coronavirus, transmitted from human to human by droplets or by direct contact. Healthcare workers (HCWs) were at high risk and accounted for a fifth of all cases globally. Risk factors for infection in HCWs included lack of awareness and preparedness when the disease first struck, poor institutional infection control measures, lack of training in infection control procedures, poor compliance with the use of personal protection equipment (PPE), exposure to high-risk procedures such as intubation and nebulization, and exposure to unsuspected SARS patients. Measures to prevent nosocomial infection included establishing isolation wards for triage, SARS patients, and step-down; training and monitoring hospital staff in infection-control procedures; active and passive screening of HCWs; enforcement of droplet and contact precautions; and compliance with the use of PPE. [References: 32]
Quote from full-text: "He was treated with antibiotics for communityacquired pneumonia but also received a bronchodilator through a jet nebulizer at a flow rate of 6 liters/min, four times daily for seven days.7 Two days after his admission, doctors and nurses who had helped in his care, and medical students who had examined him, fell ill one after another."

8. **Loeb M, McGeer A, Henry B, et al. SARS among critical care nurses, Toronto. Emerg Infect Dis. 2004;10(2):251-5. DOI: 10.3201/eid1002.030838**
To determine factors that predispose or protect healthcare workers from severe acute respiratory syndrome (SARS), we conducted a retrospective cohort study among 43 nurses who worked in two Toronto critical care units with SARS patients. Eight of 32 nurses who entered a SARS patient's room were infected. The probability of SARS infection was 6% per shift worked. Assisting during intubation, suctioning before intubation, and manipulating the oxygen mask were high-risk activities. Consistently wearing a mask (either surgical or particulate respirator type N95) while caring for a SARS patient was protective for the nurses, and consistent use of the N95 mask was more protective than not wearing a mask. Risk was reduced by consistent use of a surgical mask, but not significantly. Risk was lower with consistent use of a N95 mask than with consistent use of a surgical mask. We conclude that activities related to intubation increase SARS risk and use of a mask (particularly a N95 mask) is protective.
Quote from full-text: "We hypothesized that patient care activities (e.g., intubating, suctioning of endotracheal tubes, and administering nebulizers) that increase exposure to respiratory droplets are associated with an increased risk for SARS transmission and that masks protect against infection."

ACCESS ARTICLE URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3322898/

9. **Wan GH, Tsai YH, Wu YK, et al. A large-volume nebulizer would not be an infectious source for severe acute respiratory syndrome. Infect Control Hosp Epidemiol. 2004;25(12):1113-5.**
We attempted to detect the presence of airborne SARS-coronavirus (CoV) in a healthcare setting when a patient with SARS used a humidifier or a large-volume nebulizer (LVN). All of the air samples from the humidifier and LVN were found to have negative SARS-CoV-specific DNA products.

10. **Wong TW, Lee CK, Tam W, et al. Cluster of SARS among medical students exposed to single patient, Hong Kong. Emerg Infect Dis. 2004;10(2):269-76. DOI: 10.3201/eid1002.030452**
We studied transmission patterns of severe acute respiratory syndrome (SARS) among medical students exposed exclusively to the first SARS patient in the Prince of Wales Hospital in Hong Kong, before his illness was recognized. We conducted a retrospective cohort study of 66 medical students who visited the index patient's ward, including 16 students with SARS and 50 healthy students. The risk of contracting SARS was sevenfold greater among students who definitely visited the index case's cubicle than in those who did not (10/27 [41%] versus 1/20 [5%], relative risk 7.4; 95% confidence interval 1.0 to 53.3). Illness rates increased directly with proximity of exposure to the index case. However, four of eight students who were in the same cubicle, but were not within 1 m of the index case-patient, contracted SARS. Proximity to the index case-patient was associated with transmission, which is consistent with droplet spread. Transmission through fomites or small aerosols cannot be ruled out. Quote from Full-text: "Epidemiologic investigations indicate that this patient transmitted SARS to 47 healthcare workers on the ward to which he was admitted; the administration of a bronchodilator through a jet nebulizer was widely believed to have contributed to this dramatic pattern."
ACCESS ARTICLE URL:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3322939/pdf/03-0452.pdf

11. **Ho PL, Tang XP, Seto WH. SARS: hospital infection control and admission strategies. Respirology (Carlton, Vic). 2003;8 Suppl:S41-5. DOI: 10.1046/j.1440-1843.2003.00523.x**
Nosocomial clustering with transmission to health care workers, patients and visitors is a prominent feature of severe acute respiratory syndrome (SARS). Hospital outbreaks of SARS typically occurred within the first week after admission of the very first SARS cases when the disease was not recognized and before isolation measures were implemented. In the majority of nosocomial infections, there was a history of close contact with a SARS patient, and transmission occurred via large droplets, direct contact with infectious material or by contact with fomites contaminated by infectious material. In a few instances, potential airborne transmission was reported in association with endotracheal intubation, nebulised medications and non-invasive positive pressure ventilation of SARS patients. In all SARS-affected countries, nosocomial transmission of the disease was effectively halted by enforcement of routine standard, contact and droplet precautions in all clinical areas and additional airborne precautions in the high-risk areas. In Hong Kong, where there are few private rooms for patient isolation, some hospitals have obtained good outcome by having designated SARS teams and separate wards for patient triage, confirmed SARS cases and step-down of patients in whom SARS had been ruled out. In conclusion, SARS represents one of the new challenges for those who are involved in hospital infection control. As SARS might re-emerge, all hospitals should take advantage of the current SARS-free interval to review their infection control programmes, alert mechanisms, response capability and to repair any identified inadequacies.
ACCESS ARTICLE URL:
https://onlinelibrary.wiley.com/doi/epdf/10.1046/j.1440-1843.2003.00523.x

12.Lee N, Hui D, Wu A, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. The New England journal of medicine. 2003;348(20):1986-94. DOI: 10.1056/NEJMoa030685

BACKGROUND: There has been an outbreak of the severe acute respiratory syndrome (SARS) worldwide. We report the clinical, laboratory, and radiologic features of 138 cases of suspected SARS during a hospital outbreak in Hong Kong. METHODS: From March 11 to 25, 2003, all patients with suspected SARS after exposure to an index patient or ward were admitted to the isolation wards of the Prince of Wales Hospital. Their demographic, clinical, laboratory, and radiologic characteristics were analyzed. Clinical end points included the need for intensive care and death. Univariate and multivariate analyses were performed. RESULTS: There were 66 male patients and 72 female patients in this cohort, 69 of whom were health care workers. The most common symptoms included fever (in 100 percent of the patients); chills, rigors, or both (73.2 percent); and myalgia (60.9 percent). Cough and headache were also reported in more than 50 percent of the patients. Other common findings were lymphopenia (in 69.6 percent), thrombocytopenia (44.8 percent), and elevated lactate dehydrogenase and creatine kinase levels (71.0 percent and 32.1 percent, respectively). Peripheral air-space consolidation was commonly observed on thoracic computed tomographic scanning. A total of 32 patients (23.2 percent) were admitted to the intensive care unit; 5 patients died, all of whom had coexisting conditions. In a multivariate analysis, the independent predictors of an adverse outcome were advanced age (odds ratio per decade of life, 1.80; 95 percent confidence interval, 1.16 to 2.81; P=0.009), a high peak lactate dehydrogenase level (odds ratio per 100 U per liter, 2.09; 95 percent confidence interval, 1.28 to 3.42; P=0.003), and an absolute neutrophil count that exceeded the upper limit of the normal range on presentation (odds ratio, 1.60; 95 percent confidence interval, 1.03 to 2.50; P=0.04). CONCLUSIONS: SARS is a serious respiratory illness that led to significant morbidity and mortality in our cohort.

Quote from full-text: "However, the use of a jet nebulizer to administer aerosolized albuterol in the index patient had probably aggravated the spread of the disease by droplet infections."

12. **Tomlinson B, Cockram C. SARS: experience at Prince of Wales Hospital, Hong Kong. The Lancet. 2003;361(9368):1486-7. DOI: https://doi.org/10.1016/S0140-6736(03)13218-7**

The Prince of Wales Hospital (PWH) has been at the forefront of the outbreak of severe acute respiratory syndrome (SARS) in Hong Kong.1 We relate our experience at this hospital. A working definition of SARS is important,2 although clinical conditions rarely remain within artificial boundaries. Some patients might not have all features, others may present unusually. Fever is a cardinal symptom but not always so, and is sometimes absent in elderly patients. Some patients have presented with diarrhoea or, in at least two cases, with severe acute abdominal pain requiring exploratory laparotomy. All these patients developed typical SARS. Patients presenting with other respiratory infections must now all be regarded as potential SARS cases until proven otherwise. Contact with a known case is an important discriminator but, if emphasised too strongly in the diagnostic process, may lead to false positives or negatives.

Quote from full-text: "One important factor in the extensive dissemination of infection appears to have been the use of nebulised bronchodilator, which increased the droplet load surrounding the patient."

13. **Zhao Z, Zhang F, Xu M, et al. Description and clinical treatment of an early outbreak of severe acute respiratory syndrome (SARS) in Guangzhou, PR China. J Med Microbiol. 2003;52(8):715-20. DOI: 10.1099/jmm.0.05320-0**

Severe acute respiratory syndrome (SARS), now known to be caused by a coronavirus, probably originated in Guangdong province in southern China in late 2002. The first major outbreak occurred in Guangzhou, the capital of Guangdong, between January and March 2003. This study reviews the clinical presentation, laboratory findings and response to four different treatment protocols. Case notes and

laboratory findings were analysed and outcome measures were collected prospectively. The SARS outbreak in Guangdong province and the outbreak in Guangzhou associated with hospitals in the city are described, documenting clinical and laboratory features in a cohort of 190 patients randomly allocated to four treatment regimens. Patients were infected by close contact in either family or health-care settings, particularly following procedures likely to generate aerosols of respiratory secretions (e.g. administration of nebulized drugs and bronchoscopy). The earliest symptom was a high fever followed, in most patients, by dyspnoea, cough and myalgia, with 24% of patients complaining of diarrhoea. The most frequent chest X-ray changes were patchy consolidation with progression to bilateral bronchopneumonia over 5-10 days. Thirty-six cases developed adult respiratory distress syndrome (ARDS), of whom 11 died. There was no response to antibiotics. The best response (no deaths) was seen in the group of 60 patients receiving early high-dose steroids and nasal CPAP (continuous airway positive pressure) ventilation; the other three treatment groups had significant mortality. Cross-infection to medical and nursing staff was completely prevented in one hospital by rigid adherence to barrier precautions during contact with infected patients. The use of rapid case identification and quarantine has controlled the outbreak in Guangzhou, in which more than 350 patients have been infected. Early administration of high-dose steroids and CPAP ventilation appears to offer the best supportive treatment with a reduced mortality compared with other treatment regimens.

SEARCH STRATEGIES

CINAHL

S3 S1 AND S2 26
S2 (MH "Nebulizers and Vaporizers") OR TX nebuli* 9,522
S1 ((MH "Coronavirus+" OR MH "Coronavirus Infections+") OR (TI coronavirus* OR corona-virus* OR COVID OR SARS OR MERS) OR (AB coronavirus* OR corona-virus* OR COVID OR SARS OR MERS)) 4,992

Cochrane Library

#1 MeSH descriptor: [Coronavirus] explode all trees 11
#2 MeSH descriptor: [Severe Acute Respiratory Syndrome] explode all trees 47
#3 (coronavirus* or corona-virus* or COVID or SARS or MERS):ti,ab,kw 284
#4 #1 OR #2 OR #3 285
#5 MeSH descriptor: [Nebulizers and Vaporizers] explode all trees 2274
#6 nebuli* 5986
#7 #5 OR #6 6430
#8 #4 AND #7 2

Medline

1 exp "nebulizers and vaporizers"/or nebuli*.af. (17181)
2 exp coronavirus/ or severe acute respiratory syndrome/ or (coronavirus* or corona-virus* or COVID or SARS or MERS).mp. (21295)
3 1 and 2 (18)

PubMed

#3 (#1 AND #2) 22
#2 nebuli* 16640
#1 (2019 novel coronavirus disease OR 2019 novel coronavirus infection OR 2019-ncov disease OR 2019-ncov infection OR coronavirus disease 2019 OR coronavirus disease-19 OR coronavirus* OR coronovirus* OR coronavirus Infections OR Wuhan coronavirus OR 2019-nCoV OR COVID-19 OR CORVID-19 OR wn co OR novel

coronavirus OR new coronavirus OR 2019 novel OR new coronavirus OR ncov OR SARS-CoV-2 OR SARSCov19 OR ncov* wuhan OR SARS OR MERS OR corona-virus*) 22054

Search terms for other resources used in various combinations:

- coronavirus, COVID, SARS, MERS,
- nebulizer, nebuliser, vaporizer