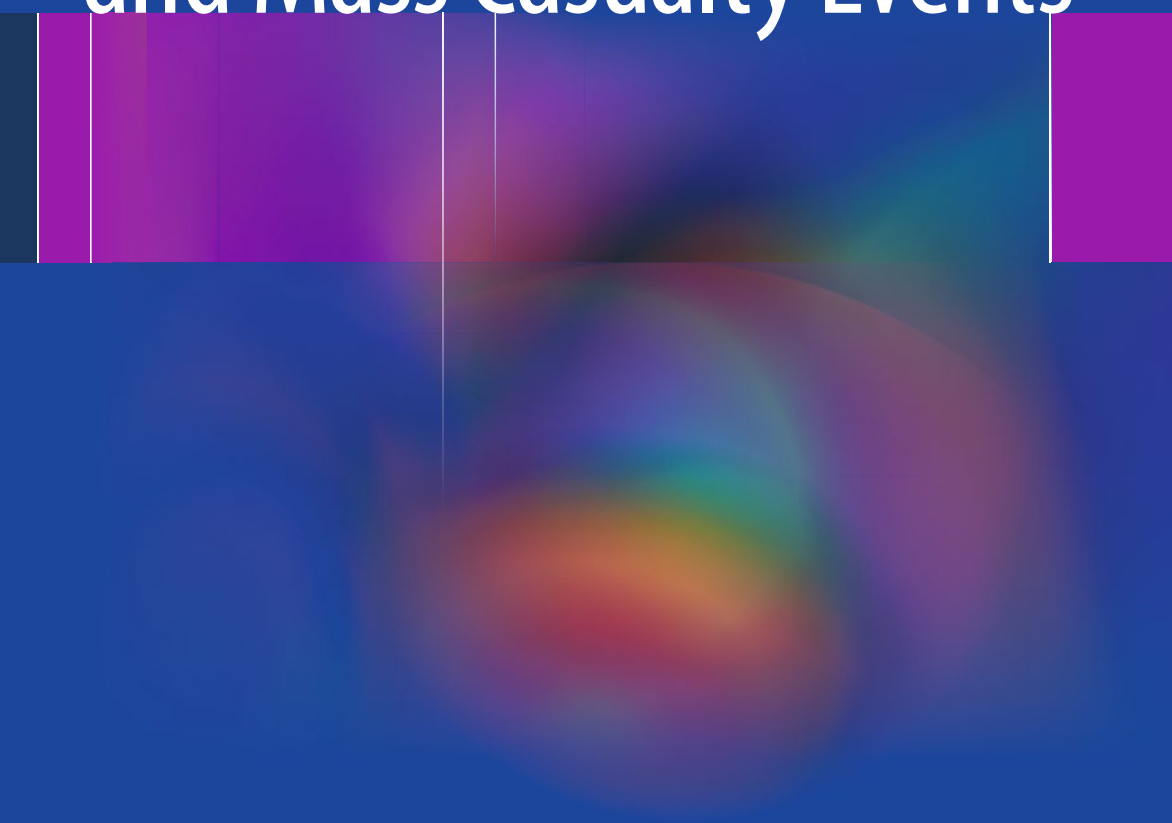
Antonio M. Esquinas *Editor*

Noninvasive Ventilation in High-Risk Infections and Mass Casualty Events



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To my wife Rosario and daughters Rosana and Alba…
my source of inspiration

Preface

Pulmonary infections represent one of the main causes of development of severe acute respiratory insufficiency that requires hospital admission in pneumology wards and intensive care units. In this scenario, mechanical ventilation is cornerstone in severe forms.

However, some types of pulmonary infections are characterized by severity and high risk of contamination, especially for health personnel and debilitated critically ill patients. These high-risk pulmonary infections are characterized by their great capacity for rapid spread and mortality, as determined in the current and past pandemics as SARS, swine flu and the classical outbreak infections of pulmonary tuberculosis or legionella pneumophila. Lastly, some forms of bioterrorism and biochemical agents have been added as new potential source of acute respiratory failure affecting a great number of patients.

This is a continuum and permanent challenge to resolve to Emergency Medicine, Pneumology and Critical Care Medicine community.

In this last decade selection of more appropriate non-invasive therapeutic options may avoid complications associated with invasive mechanical ventilation as ventilator associated pneumonia and prolonged mechanical ventilation. In this scenario, non-invasive mechanical ventilation has been shown as growing practical and safe alternative.

However, there are no practical books that define appropriate criterias for selection, contraindications and rational preventive programs for pre and hospital health organization. In this book entitled *Noninvasive Ventilation in High-Risk Infections and Mass Causalities*, we discuss from a practical point of view, what is the role of non-invasive mechanical ventilation, best hospital organizational recommendations, protection mechanisms and patient care during non-invasive mechanical ventilation in patients suffering high-risk pulmonary infections and mass causalities.

Murcia, Spain — Antonio M. Esquinas

Acknowledgement

Thanks to all authors who have believed in this project and have made a huge effort to develop the content of these chapters, masterfully by combining science and practice. Without them we would never have been possible to develop this work.

To all patients we treat every day; they are part of this effort to encourage us to think that this book was necessary.

Contents

Abbreviations

ACPO	Acute cardiogenic pulmonary oedema
AGP	Aerosol generating procedures
AHRF	Acute hypoxemic respiratory failure
AIDS	Acquired immunodeficiency syndrome
ALI	Acute lung injury
APACHE II	Acute Physiology and Chronic Health Evaluation II
APRV	Release airway pressure ventilation
ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
ARF	Acute hypoxemic respiratory failure
ASB	Assisted spontaneous breathing
ATS	American Thoracic Society
AVAPS	Average volume assured pressure support
BAL	Bronchoalveolar lavage
BAS	Broncoaspiration
BiPAP	Bilevel nasal positive system
BiPAP (S/T)	Bilevel positive airway pressure (spontaneous/timed)
BTS	British Thoracic Society
CAP	Community Acquired Pneumonia
CDC	Center for Disease Control
CMV	Cytomegalovirus
CMV	Conventional mechanical ventilation
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous positive airway pressure
C_{rs}	Low respiratory system compliance
CT	Computed tomography
DAMPs	Danger associated molecular patterns
DPI	Days post inoculation
ECMO	Extracorporeal membrane oxygenation
EPAP	Expiratory positive airway pressure
ERS	European Respiratory Society
ESICM	European Society of intensive medicine
ETI	Endotracheal intubation

ETT	Endotracheal tube
EU FFP2	European Union Filtering Face-piece class 2
EVT	Exhaled tidal volume
FB	Fiberoptic bronchoscopy
FC	Flail chest
FiO_2	Inspired fraction of oxygen
FRC	Functional residual capacity
GRADE	Grading of Recommendations Assessment, Development and Evaluation
H1N1pdm09	Pandemic 2009 influenza A (H1N1) virus
HAART	Highly Active Antiretroviral Therapy
HCWs	Health care workers
HFC	High flux cannula
HFNC	High-flow nasal cannula
HH	Heated humidifier
HIV/AIDS	human immunodeficiency virus/acquired immunodeficiency syndrome
HME	Heat and moisture exchanger
HPS	Human simulator patient
ICU	Intensive Care Unit
IDSA	Infectious Diseases Society of America
ILV	Independent lung ventilation
IMV	Invasive mechanical ventilation
IPAP	Inspiratory positive airway pressure
ISB	Isothermic saturation boundary
ISO	International organization for standardization
ISS	Injury Severity Score
IV	Invasive ventilation
LFNC	Low-flow nasal cannulas
LM	Laryngeal mask
LRTI	Low respiratory tract infection
Ml/kg	Milliliters per kilogram
MOF	Multiorgan failure
MV	Mechanical ventilation
mWCAS	Modified Wilson clinical asthma score
NAVA	Neurally adjusted ventilatory assist
NIMV	Noninvasive mechanical ventilation
NIPPV	Non-Invasive Positive Pressure Ventilation
NIV	Non-invasive ventilation
NP	Nosocomial infection
PaO_2	Partial pressure of oxygen in arterial blood
PaO_2/FIO_2 ratio	Blood oxygen partial pressure/inspired oxygen fraction ratio
PBS	Protected brush specimen
PC	Pulmonary contusion

PCO_2	Carbon dioxide partial pressure
Pdi	Transdiaphragmatic pressure
PED	Pediatric emergency department
PEEP	Positive end expiratory pressure
P_{es}	Esophageal pressure
PICU	Pediatric intensive care unit
PIP	Peak inspiratory pressure
PMNs	Polymorphonuclear leukocytes
PPE	Personal Protective Equipment
PSV	Pressure Support Ventilation
PTP	Pressure time product
PTP di	Diaphragm pressure time product
RCTs	Randomized controlled trials
RH	Relative humidity
RHDCU	Respiratory high-dependency units
RR	Respiratory rate
RSV	Respiratory syncytial virus
SaO_2	Oxygen hemoglobin saturation
SAPS II	Simplified Acute Physiology Score
SARS	Severe acute respiratory syndrome
SARS-CoV	Severe acute respiratory syndrome-Coronavirus
SEMICYUC	Sociedad Española de Medicina Intensiva y Unidades Coronarias
TB	Tuberculosis
TBLB	Transbronchial lung biopsy
TLC	Total lung capacity
TNF α	Tumor Necrosis Factor α
UK	United Kingdom
US NIOSH	United States National Institute for Occupational Safety and Health
VA	Ventilatory assistance
VAP	Ventilator-Associated Pneumonia
VEGF	Vascular Endothelial Growth Factor
Vt	Tidal Volume
VZV	Varicella Zoster virus
WHO	World Health Organization
WOB	Work of breathing

Part I

Rationale and Equipment

High-Risk Infections: Influence of Down-Regulation and Up-Regulation of Cough Using Airway Reflexes and Breathing Maneuvers

1

Zoltan Tomori and Viliam Donic

Keywords

Acute respiratory failure • Aspiration pneumonia • Aspiration reflex • Expiration reflex • Coughing • Flu A (H1N1) • Breathing maneuvers

Coughing is a watchdog of the lungs. It represents the most important airway defensive reflex and one of the main symptoms of respiratory disease. During coughing and sneezing, particles of mucus can be expelled for a distance of up to 9 m [1]. Various pathogens, if present, may therefore infect nearby people and animals, contributing to massive dissemination of airborne infections. In addition to using various protective measures, down-regulation of coughing plays a substantial role in preventing dissemination of respiratory infections. For example, about 80 % of passengers on a 3-h airplane trip may be infected by the cough of an individual carrying the flu virus. These newly infected passengers then disseminate the viral infection at their destinations worldwide.

Protective and therapeutic actions are particularly urgent during a pandemic of influenza A (H1N1 virus), which mainly affects the most marginal and immunocompromised members of a population, including children. There are several pathophysiological forms of cough down-regulation [2] that can be applied during a flu pandemic.

The *D222G* mutation of the 2009 pandemic virus A (H1N1) caused destruction of the tracheobronchial ciliated cells as well as the bronchiolar and alveolar cells. This, in turn, disabled the clearing mechanisms of the lungs, which in Spain caused a 3.5-fold increase in the fatal outcome of the 2009 flu pandemic [3, 4].

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During the breathing cycle, the lung volume at the moment determines the actions of two alternating tendencies—inspiration and expiration—mediated by two distinct ventilatory reflexes. The reflexes are induced by stimulation of the airway and lung receptors, again depending on the lung volume and local pressure at the moment. At the early phase of inspiration, the lung volume is very low, just starting to increase gradually from its functional residual capacity (FRC). There is a strong general tendency to inspire at this point [5].

Inspiratory efforts can be provoked by various methods for stimulating airway rapidly adapting receptors (RARs). In cats, rapid inspiratory efforts can be evoked by nasopharyngeal stimulation, manifesting as the sniff- and gasp-like aspiration reflex (AspR) [1, 6–8] and by rapid lung inflation [5], which decreases the frequency and intensity of the subsequent expiratory efforts of cough and postpones them [9]. During gastroesophageal reflux or inhalation of irritant substances to the larynx, there is a strong "urge to cough" that can be voluntarily suppressed. To prevent aspiration of irritant substances into the lower airways, the necessary effort of coughing may be postponed by a previous, very slow voluntary inspiration followed by breath-holding and swallowing of the bolus to the esophagus. Only then can the effort to cough be initiated for expulsion of irritants from the airways [10–12]. Similar voluntary cough suppression commonly decreases the disturbing effect of coughing during a concert. It can similarly strongly inhibit dissemination of airborne infections due to coughing. Such ventilatory maneuvers might be usefully applied to the fight against flu pandemics and other widespread respiratory infection outbreaks.

On the other hand, the increasing lung volume at and above the tidal volume (V_T) stimulates the slowly adapting receptors (SARs). Also, because of the Hering Breuer inspiration inhibiting reflex (HBIIR), after inspiratory "switch-off" the V_T induces the expiratory phase. The tendency to expire is strong at the end of tidal inspiration [5]. Therefore, stimulation of laryngeal RARs interrupts the inspiration and evokes laryngoconstriction and the expiration reflex (ExpR) [1, 7, 8]. Additionally, an inspired or inflated volume above the normal V_T or blockade of lung deflation at the beginning of expiration by positive pressure can adequately speed up and increase the intensity of the subsequent expiratory effort. It is caused by stimulation of airway receptors and manifests as the Hering Breuer expiration facilitating reflex (HBEFR) [5].

Hyperinflation or occlusion of airways and hindering lung deflation by a ventilator or a pressure pulse provokes the ExpR and the cough reflex (CR). Such rapid expiratory efforts might promote expulsion of infected mucus, preventing its protrusion from the larynx to the lungs and preclude, or at least postpone, the development of dangerous aspiration pneumonia [13]. A proposed voluntary breathing maneuver consists of several rapid sniffs with a closed mouth of 0.5 s duration, each followed by forced expiration lasting about 3 s. Such a maneuver might save many lives and improve the quality of life of millions of people worldwide during imminent flu pandemics or other widespread respiratory infections. The early inspiratory sniffs and other spasmodic inspirations, including provocation of the AspR, result in down-regulation of coughing and may substantially retard a flu or other respiratory infection pandemic.

Rapid reflex or voluntary hyperinflation or occluded lung deflation—started at the early expiratory phase by pressure pulses—may result in reflex up-regulation of cough due to stimulation of airway receptors and mediated by HBEFR [5]. Such up-regulation may prevent, or at least postpone, the development of mostly fatal aspiration pneumonia. The sniff- and gasp-like AspR provoked by nasopharyngeal stimulation in anesthetized cats decreased the number and intensity of cough efforts provoked in the tracheobronchial region [9]. Similarly, the urge to cough may be suppressed, and even the motor act of coughing might be inhibited or at least postponed by voluntary action, helping to decrease the dissemination of airborne infections [11, 12]. Rapid, deep breaths through the nose, but not through the mouth, have bronchoprotective and bronchospasmolytic effects in probands and patients with mild bronchial asthma. This bronchoprotective effect in humans requires rapid inspiratory airflow [14, 15]. The sniff-like voluntary inspiration decreases the bronchoconstriction detected by one-second forced expiratory volume (FEV_1), induced by metacholine inhalation in adult asthmatics [16] and decreased the number of coughs provoked by capsaicin inhalation in young asthmatics [17]. These results indicate a reflex origin of the bronchodilator effect of nasopharyngeal stimulation, which decreases in parallel with bronchodilation and bronchoconstrictor-triggered coughing [18]. Taking advantage of voluntary airway reflexes and ventilatory maneuvers have many important practical applications [19]. They include detection of preparatory movement activity in the premotor area in persons in a vegetative state [20, 21]. The control of wheelchairs by trained paraplegics [22] can be reproduced by voluntary performance of aspiration and expiration reflexes, representing binary signals [19]. Gasping respiration developing in animals can provide autoresuscitation for few minutes even during cardiac arrest [23]. Therefore, provocation of the gasp-like AspR persisting even in agonal state or voluntary sniffs, might provide autoresuscitation in emergency situations [7, 19].

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Noninvasive Mechanical Ventilation: Models to Assess Air and Particle Dispersion

2

David S.C. Hui

Keywords
Exhaled air • Dispersion • NIV • Influenza • SARS

2.1 Introduction

Respiratory failure is a major complication of viral infections such as severe acute respiratory syndrome (SARS) [1], avian influenza H5N1 infection [2], and the 2009 pandemic influenza (H1N1) infection [3]. The course may progress rapidly to acute respiratory distress syndrome (ARDS) and multi-organ failure, requiring intensive care. Noninvasive ventilation (NIV) may play a supportive role in patients with severe viral pneumonia and early ARDS/acute lung injury. It can act as a bridge to invasive mechanical ventilation, although it is contraindicated in critically ill patients with hemodynamic instability and multi-organ dysfunction syndrome [4]. Transmission of some of these viral infections can convert from droplets to airborne during respiratory therapy.

During the major outbreak of SARS, endotracheal intubation [5], oxygen therapy, and NIV were found to be risk factors for major nosocomial outbreaks affecting health care workers [6]. Possible aerosol transmission during a nosocomial outbreak of seasonal influenza was temporally related to the application of NIV in an index patient with hypercapnic respiratory failure due to acute exacerbation of chronic obstructive pulmonary disease (COPD). The patient was on a medical ward with an imbalanced indoor airflow [7]. As influenza virus may be contained in fine

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particles generated during tidal breathing [8], NIV may disperse potentially infected aerosols, especially when patients cough and sneeze frequently, contributing to nosocomial transmission of influenza. Pulmonary tuberculosis (TB) is well known to spread by the airborne route. A recent study showed that a small number of patients with pulmonary TB (28 %) produced culturable cough aerosols [9].

Thus, it is important to examine the exhaled air directions and dispersion distances during application of NIV to patients with respiratory failure via commonly used face masks. The data can improve our understanding of and knowledge about infection control. Such knowledge can facilitate the development of preventive measures to reduce the risk of nosocomial transmission during application of NIV to high-risk patients with respiratory infections.

2.2 Methods

As there is no reliable, safe marker that can be introduced into human lungs for experimental purposes, the laser smoke visualization method and the human patient simulator (HPS) model have been adopted as the method for studying exhaled air dispersion during application of various types of respiratory therapy in hospital medical wards, including the negative-pressure isolation room [10–13].

2.2.1 NIV and Lung Model

The HPS represents a 70-kg adult man sitting on a 45°-inclined hospital bed (Fig. 2.1). The HPS contains a realistic airway and is programmed to remove oxygen and inject carbon dioxide into the system according to a preset respiratory exchange ratio and oxygen consumption. The lung compliance can also be changed to simulate different degrees of lung injury during chest infection. By varying the oxygen consumption (200, 300, and 500 ml/min) and lung compliance (70, 35, and 10 ml/cmH_2O), these sets of values produce a range of tidal volumes, respiratory rates, and peak inspiratory flow similar to those of patients with minimal (essentially normal lung function), moderate, or severe lung injury, respectively. For example, lung compliance is set at 35 ml/cm H_2O and oxygen consumption at 300 ml/min to mimic mild lung injury. Tidal volume and respiratory rate are regulated so a respiratory exchange ratio of 0.8 is maintained during measurements. Typically, this is achieved with a tidal volume of 300 ml and a respiratory rate of 25 breaths/min [10–13]. Lung compliance and airway resistance also responds in a realistic manner to relevant respiratory challenges. The HPS produces an airflow pattern that is close to the in vivo situation. It has been applied in previous studies to simulate human respiration [14–17].

Deliberate leakage from the exhalation ports of the Mirage mask (ResMed, Bella Vista, NSW, Australia) [10], ComfortFull 2, and Image 3 masks (Respironics, Murrysville, PA, USA) [11] firmly attached to a high-fidelity HPS (HPS 6.1; Medical Education Technologies, Sarasota, FL, USA) has been evaluated. NIV was

Fig. 2.1 Human patient simulator (HPS) lying at 45° on a bed undergoing noninvasive ventilation via the ResMed Mirage face mask. A laser beam located on the right side of the bed lateral to the human patient simulator illuminates the exhaled air particles leaking from the exhalation ports of the face mask in the coronal plane. A camera was positioned along the sagittal plane at the end of the bed to capture lateral dispersion of exhaled air illuminated by the laser device. Positions of the camera and the laser device would be exchanged when the exhaled air dispersion from the face mask is examined along the sagittal plane

applied using a bilevel positive airway pressure device (VPAP III ST; ResMed) via each mask. The inspiratory positive airway pressure (IPAP) was initially set at 10 cmH_2O and gradually increased to 18 cmH_2O. The expiratory positive airway pressure (EPAP) was maintained at 4 cmH_2O throughout the study [10, 11].

2.2.2 Flow Visualization

Visualization of airflow around each NIV face mask was facilitated by marking the air with smoke particles produced by a M-6000 smoke generator (N19; DS Electronics, Sydney, Australia), as in our previous studies [10–13]. The oil-based smoke particles, measuring less than 1 μm in diameter, are known to follow the airflow pattern precisely with negligible slip [18]. The smoke was introduced continuously to the right main bronchus of the HPS. It mixed with alveolar gas and then was exhaled through the airway. Sections through the leakage jet plume were then revealed by a thin, green laser light sheet (532 nm wavelength, continuous-wave

mode) created by a diode-pumped solid-state laser (OEM UGH-800 mW; Lambda Pro Technologies, Shanghai, China) with custom cylindrical optics to generate a two-dimensional laser light sheet [10–13].

The light sheet was initially positioned in the median sagittal plane of the HPS and subsequently shifted to paramedian sagittal planes. This allowed us to investigate the regions directly above and lateral to the mask and the patient [10–13].

All leakage jet plume images revealed by the laser light sheet were captured by a high-definition video camera—Sony high-definition digital video camcorder (HDR-SR8E; Sony, Tokyo, Japan); ClearVid complementary metal oxide semiconductor sensor (Sony) with a Carl Zeiss Vario-Sonnar T* Lens (Carl Zeiss, Jena, Germany)—with optical resolution of 1,440 × 1,080 pixels per video frame. The normalized smoke concentration in the plume was estimated from the light intensity scattered by the smoke particles [10–13].

2.2.3 Image Analysis

The normalized smoke concentration in the mask leakage air was estimated from the light scattered by the particles. The analysis was based on scattered light intensity being proportional to the particle concentration under the special conditions of constant-intensity laser light sheet illumination and monodispersion of small (submicron) particles [18]. In short, the thin laser light sheet of near-constant intensity illuminated the smoke particle markers in the mask airflow leakage. Smoke particles scattered laser light perpendicular to the light sheet. The pictures were then collected and integrated by the video camera element and lens [10–13].

2.2.4 Image Capture and Frame Extraction

A motion video of at least 20 breathing cycles for each NIV setting was captured and individual frames extracted as gray-scale bitmaps for intensity analysis. Frames were extracted at time points starting from the beginning of each inspiration to generate an ensemble average for the corresponding instant of the respiratory cycle [10–13]. The time at which the normalized concentration contours spread over the widest region from the NIV mask was chosen for the ensemble average to estimate the greatest dispersion distance. This was found to be approximately at the mid-respiratory cycle [10, 11].

2.2.5 Intensity Averaging and Concentration Normalization

All gray-scale frames were read into a program specifically developed for these studies [10–13] (MathCad 8.0; MathSoft, Cambridge, MA, USA) [19] along with the background intensity images obtained with the laser switched off. The background intensity image was subtracted from each frame, pixel by pixel, to remove any stray background light. The pixel intensity values were averaged over all frames

to determine the average intensity. The resulting image was the total intensity of light scattered perpendicular to the light sheet by the smoke particles. It was directly proportional to the smoke concentration under the conditions mentioned above. The image was normalized against the highest intensity found within the leakage jet plume to generate normalized particle concentration contours [10–13].

As the smoke particles marked air that originated from the HPS's airways before leaking from the mask, the concentration contours effectively represent the probability of encountering air around the patient that has come from within the mask and the patient's respiratory system. The normalized concentration contours are made up of data collected from at least 20 breaths. A contour value of 1 indicates a region that consists entirely of air exhaled by the patient, where there is a high chance of exposure to the exhaled air, such as at the mask exhaust vents. A value near 0 indicates no measurable air leakage in the region and a small chance of exposure to the exhaled air [10–13].

2.3 Results

The results are presented with reference to the median sagittal plane.

2.3.1 Noninvasive Positive-Pressure Ventilation Applied via the ResMed Mirage Mask

With the ResMed Mirage mask, a jet plume of air escaped through the exhaust holes to a distance of approximately 0.25 m radially during application of IPAP 10 cmH_2O, with some leakage from the nasal bridge. The leakage jet probability was highest about 60–80 mm lateral to the sagittal plane of the HPS. Without nasal bridge leakage, the plume jet from the exhaust holes increased to a 0.40 m radius circle, and exposure probability was highest about 0.28 m above the patient. When IPAP was increased to 18 cmH_2O, the vertical plume extended to about 0.5 m above the patient and the mask, with some horizontal spread along the ward roof [10].

2.3.2 Noninvasive Positive-Pressure Ventilation Applied via the ComfortFull 2 Mask

With the ComfortFull 2 mask, a vertical, cone-shaped plume leaked out from the mask exhalation diffuser and propagated well above and almost perpendicular to the patient at an IPAP and an EPAP of 10 and 4 cmH_2O, respectively. The maximum dispersion distance of smoke particles—defined as the boundary with a region encountering <5 % normalized concentration of exhaled air (light blue contour smoke concentration scale)—was 0.65 m, whereas that of a high concentration (containing >75 % normalized concentration of exhaled air, red zone, and above) was 0.36 m. There was no significant room contamination by exhaled air (as reflected by the blue background in the isolation room) other than the exhalation jet plume [11].

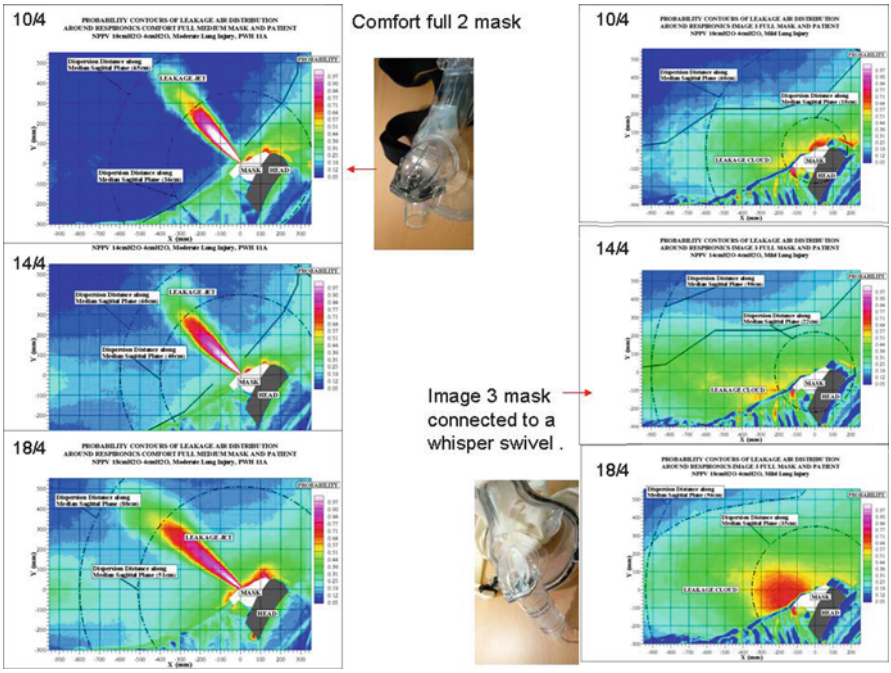

Fig. 2.2 Exhaled air dispersion along the median sagittal plane when the recumbent HPS was wearing the Comfortfull 2 mask (images on the *left*) or the Image 3 mask connected to the whisper swivel (images on the *right*) when the inspiratory positive airway pressure was increased from 10 to 14 and then 18 cmH_2O while the expiratory positive airway pressure was fixed at 4 cmH_2O [11]

When the IPAP was increased from 10 to 14 cmH_2O, the maximum exhaled dispersion distance of low-concentration exhaled air was similar at 0.65 m, but that of high-concentration exhaled air increased to 0.40 m, with contamination of the isolation room. Also, there was some exhaled air concentration outside the exhalation jet plume. When IPAP was increased to 18 cmH_2O, the dispersion distance of low-concentration exhaled air was 0.85 m, whereas that of high-concentration exhaled air increased to 0.51 m along the median sagittal plane. More background contamination of the isolation room by smoke particles was noted at higher IPAPs owing to interaction between the downstream ceiling-mounted ventilation vent and the upstream exhaled air from the HPS (images at left in Fig. 2.2) [11].

2.3.3 Noninvasive Positive-Pressure Ventilation Applied via the Image 3 Mask Connected to the Whisper Swivel

The Image 3 mask required an additional exhalation device (whisper swivel) to prevent carbon dioxide rebreathing. The exhaled air leakage was much more diffuse than that with the ComfortFull 2 mask because of the downstream leakage of

exhaled air through the whisper swivel exhalation port. At an IPAP of 10 cmH_2O, the maximum dispersion distance of a low concentration in exhaled air (light blue zone on the smoke concentration scale) was 0.95 m toward the end of the bed, whereas that of a medium concentration (containing >50 % of the normalized concentration of exhaled air, green zone, and above) was about 0.6 m along the median sagittal plane. As the IPAP was increased from 10 to 14 cmH_2O, the exhaled air with a medium concentration increased to 0.95 m toward the end of the bed along the median sagittal plane of the HPS [11].

When the IPAP was increased to 18 cmH_2O, the exhaled air with a low concentration dispersed diffusely to fill up most of the isolation room (i.e., beyond 0.95 m, as captured by the camera), whereas that with a medium concentration, occupying wider air space, was noted to spread 0.8 m toward the end of the bed, with accumulation of a high concentration of exhaled air (red zone on scale) within 0.34 m from the center of the mask, along the median sagittal plane of the HPS (images on the right in Fig. 2.2) [11].

2.4 Discussion

There is no reliable, safe marker that can be introduced into human lungs for experimental purposes. Hence, the maximum distribution of exhaled air, marked by very fine smoke particles, from the HPS during application of NIV using three face masks was examined by the laser smoke visualization method on a high-fidelity HPS model. The studies showed that the maximum distances of exhaled air particle dispersion from patients undergoing NIV with the ResMed Ultra Mirage mask was 0.5 m along the exhalation port [10]. In contrast, the dispersion distances of a low, normalized concentration of exhaled air through the ComfortFull 2 mask exhalation diffuser increased from 0.65 to 0.85 m at a direction perpendicular to the head of the HPS along the sagittal plane when IPAP was increased from 10 to 18 cmH_2O. There was also more background contamination of the isolation room at the higher IPAP [11]. Even when a low IPAP of 10 cmH_2O was applied to the HPS via the Image 3 mask connected to the whisper swivel exhalation port, the exhaled air leaked far more diffusely than from the ComfortFull 2 mask, dispersing a low normalized concentration of 0.95 m along the median sagittal plane of the HPS. The higher IPAP resulted in wider spread of a higher normalized concentration of smoke around the HPS in the isolation room with negative pressure [11].

Simonds et al. [20] applied the laser visualization method to assess droplet dispersion during application of NIV in humans with an optical particle sizer (Aerotrak 8220; TSI Instruments, High Wycombe, UK) and showed NIV as a droplet- (not aerosol-) generating procedure, producing droplets measuring >10 μm. Most of them fell onto local surfaces within 1 m of the patient.

Noninvasive ventilation is an effective treatment for patients with respiratory failure due to COPD, acute cardiogenic pulmonary edema, or pneumonia in immunocompromised patients. However, evidence supporting its use in patients with pneumonia is limited. NIV was applied to patients with severe pneumonia caused by

a 2009 pandemic influenza (H1N1) infection with a success rate of about 41 %. Although there were no reported nosocomial infections [21], there is a potential risk of applying NIV to patients hospitalized with viral pneumonia on a crowded medical ward with inadequate air changes [7]. In this regard, deliberate leakage via the exhalation ports may generate droplet nuclei and disperse infective aerosols through evaporation of water content of respiratory droplets, resulting in a superspreading event. Nonetheless, NIV was applied using a single circuit to treat patients effectively with respiratory failure due to SARS in hospitals with good infection control measures (including installation of powerful exhaust fans to improve the room air change rate and good protective personal equipment at a level against airborne infection). There were no nosocomial infections among the health care workers involved [22, 23]. In contrast, a case–control study involving patients in 124 medical wards of 26 hospitals in Guangzhou and Hong Kong identified the need for oxygen therapy and use of NIV as independent risk factors for superspread of nosocomial SARS outbreaks [6]. Similarly, a systematic review has shown a strong association between ventilation, air movement in buildings, and airborne transmission of infectious diseases such as measles, tuberculosis, chickenpox, influenza, smallpox, and SARS [24].

These studies of infection with the HPS model [10, 11] and in humans [20] have important clinical implications for preventing future nosocomial outbreaks of SARS and other highly infectious conditions such as pandemic influenza when NIV is provided. NIV should be applied in patients with severe community acquired pneumonia only if there is adequate protection for health care workers because of the potential risk of transmission via deliberate or accidental mask interface leakage and flow compensation causing dispersion of a contaminated aerosol [10, 11]. Pressure necrosis may develop in the skin around the nasal bridge if the NIV mask is applied tightly for a prolonged period of time. Many patients loosen the mask strap to relieve discomfort. Air leakage from the nasal bridge is definitely a potential means of transmitting viral infections. Fitting a mask carefully is important for successful, safe application of NIV. Addition of a viral/bacterial filter to the breathing system of NIV, between the mask and the exhalation port, or using a dual-circuit NIV via full face mask or helmet without heated humidification may reduce the risk of nosocomial transmission of a viral infection [11, 25].

In view of the observation that higher ventilator pressures result in wider dispersion of exhaled air and more air leakage [10, 11], it is advisable to start NIV with a low IPAP (8–10 cmH_2O) and increase it gradually as necessary. The whisper swivel is an efficient exhalation device to prevent carbon dioxide rebreathing, but it would not be advisable to use such an exhalation port in patients with febrile respiratory illness of unknown etiology. This is especially true in the setting of an influenza pandemic with the high potential of human-to-human transmission for fear of causing a major outbreak of nosocomial infections. It is also important to avoid the use of high IPAP, which could lead to wider distribution of exhaled air and substantial room contamination [11].

There are some limitations regarding the use of smoke particles as markers for exhaled air. The inertia and weight of large droplets in an air-droplet two-phase flow would certainly cause them to have less horizontal dispersion than occurs with the continuous air carrier phase during which the particles travel with increased inertia and drag. However, evaporation of the water content of some respiratory droplets

during coughing or sneezing when exposed to NIV may produce droplet nuclei suspended in air, whereas the large droplets fall to the ground in a trajectory pathway [10–13]. As smoke particles mark the continuous air phase, the data contours described refer to exhaled air. The results would therefore represent the "upper bound" estimates for dispersion of the droplets—which would be expected to follow a shorter trajectory than an air jet due to gravitational effects—but not fully reflect the risk of large-droplet transmission [10–13].

In summary, the laser visualization technique using smoke particles as a marker in the HPS model is a feasible means of assessing exhaled air dispersion during application of NIV and other modes of respiratory therapy [10–13]. Substantial exposure to exhaled air occurs within 1 m of patients undergoing NIV in an isolation room with negative pressure via the ComfortFull 2 mask and the Image 3 mask connected to the whisper swivel exhalation port. It must be noted that there is far more extensive leakage and room contamination with the Image 3 mask, especially at higher IPAPs [11].

Health care workers should take adequate precautions for infection control. They especially must pay attention to environmental air changes when providing NIV support to patients with severe pneumonia of unknown etiology complicated by respiratory failure.

Key Major Recommendations

- The laser visualization technique using smoke particles as markers in the HPS model is a feasible means of assessing exhaled air dispersion during application of NIV and other modes of respiratory therapy.
- Substantial exposure to exhaled air occurs within 1 m of patients undergoing NIV even in an isolation room with negative pressure.
- During application of NIV, it is advisable to choose face masks with predictable exhaled air directions and distances through the exhalation port without addition of the whisper swivel device.
- It is important to avoid using high inspiratory pressures and any face mask that requires connection to the whisper swivel exhalation port as they would lead to wider distribution of exhaled air and substantial room contamination.

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Interfaces for Noninvasive Ventilation: General Elements and Options

3

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Keywords
Interface • Non invasive ventilation

3.1 Introduction

Noninvasive ventilation (NIV) interfaces are devices that allow the ventilator's conduits to be connected with the patient's face. Adequate performances of these interface devices are vital for fulfillment of the primary objective of successful NIV. Simply put, NIV is a technique for providing ventilation without the use of an artificial airway. The search for a perfect interface started concurrently with the beginning of the era of positive-pressure noninvasive ventilation. It seems unlikely that we will ever devise an interface that would, in spirit, proclaim itself as "one size fits all."

This chapter provides a broad outline for selecting an appropriate interface device according to the specific clinical scenario and predilection of the patient. While dealing with noninvasive ventilation in day-to-day practice, one comes face to face with a number of limitations. Keeping them in mind, one realizes that NIV could be a tribulation as well as a bonus if our understanding of the practical aspects of these interface devices is not up to the mark or in depth. Such detailed understanding might seem a trivial matter, but it plays a significant role when it comes to saving a patient from NIV failure versus having to switch to invasive ventilation.

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Table 3.1 Interfaces for noninvasive ventilation

Nasal mask
Oronasal mask
Total face mask
Nasal pillow
Noninvasive ventilation (NIV) helmet
Custom-built and hybrids

Box 3.1 Requisites of an Ideal Interface

- It must be compatible with the ventilator, free from air leaks, and comfortable for the user.
- It should offer minimal resistance to the airflow and should not add to the existing dead space.
- It should have an anti-asphyxia valve to allow the patient to breathe room air in case the ventilator fails.
- It should be easy to clean, cost-effective, and durable.
- It should not produce trauma and should be simple to apply without being able to become displaced.
- It should be accompanied with a securing system that is easy to fasten.

3.2 Selecting the Interface for NIV

Once a patient fits within the configuration of the definitive indications for noninvasive mechanical ventilation and has no contraindications, the first step is to describe the breathing support to the patient and explain its various benefits. After obtaining written informed consent from the patient for NIV, we select the most appropriate interface for fulfilling the goal of successful NIV. Table 3.1 lists the various NIV interfaces that are available.

The difference in the type of interface is primarily determined by the portion(s) of the patient's face covered by the interface. For instance, the nasal mask covers only the nose, whereas the facial mask covers both the nose and the mouth. The nasal pillow, which is smaller than the nasal mask, consists of two cushions that fit under the nose. The NIV helmet covers the entire head without coming in direct contact with the face. The requisites of an ideal interface are outlined in Box 3.1.

3.3 Advantage and Disadvantages of the Various Interfaces

Various advantages and disadvantages of the interface determine selection of a device in a specific clinical scenario so it can be tailored to the individual patient. The nasal mask (Figs. 3.1 and 3.2), by virtue of covering only the nose, is easy to fit and allows speaking, drinking, and coughing. The risk of aspiration is much lower than it is with a face mask, but the chance of an air leak is higher in case the

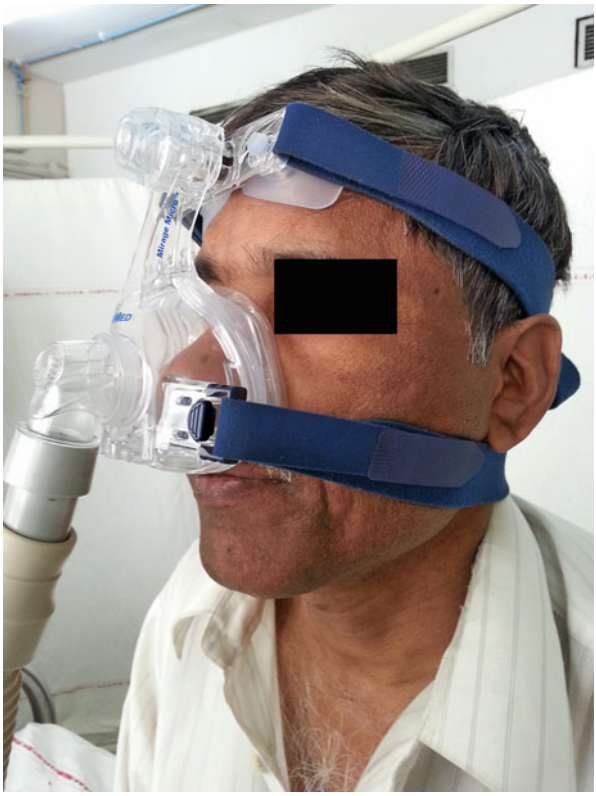

Fig. 3.1 Nasal masks cover the nose. They predispose to air leaks if placed on a mouth breather

mouth remains open. Because it is placed over the nose, its use is associated with skin irritation and ulcers. To minimize air leaks in mouth breathers, the use of a full-face mask (Figs. 3.3 and 3.4) would be apt. However, employing a face mask predisposes the patient to increased risk of aspiration and claustrophobia. Also, speaking and coughing are challenging. Similar to nasal masks, the use of nasal pillows (Figs. 3.5 and 3.6) allows speaking, drinking, and coughing. It appears to be a less claustrophobic choice. Unlike with the nasal mask, the risk of pressure sores and erythema over the nose and the nasal bridge is minimal. It does predispose to leaks in case the patient is a mouth breather. The skin trauma that can develop with full-face/nasal masks can be avoided by using an NIV helmet, which minimizes air leaks and requires minimal cooperation from the patient. The NIV helmet, however, may lead to axillary skin damage and CO_2 rebreathing.

There are concerns regarding the additional dead space created by interface devices. Despite the fact that these devices have different internal volumes, there is no increase in the dead space when the patient is on the bilevel positive airway pressure/continuous positive airway pressure (BiPAP/CPAP) mode of ventilation [1]. Therefore, when treating patients with acute respiratory failure, the different static volumes of the interfaces should not influence their selection [2].

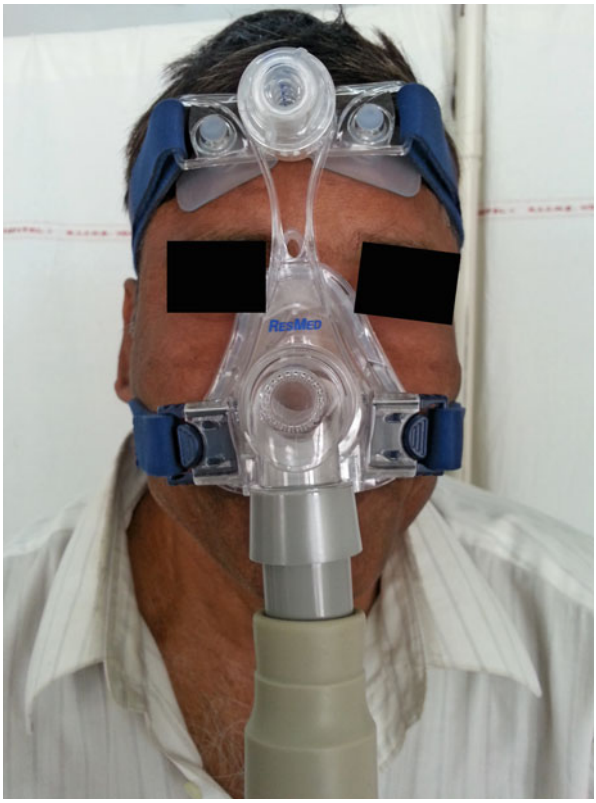

Fig. 3.2 Nasal mask. It is less claustrophobic than a full-face mask

For short-term use, the patient often breathes through the mouth. Therefore, a mask that covers the mouth, such as a full face mask or an oronasal mask (Figs. 3.7 and 3.8), would be appropriate. One study reported similar results with the use of these masks [3]. For long-term use, the choice would be more about patient comfort so long as the interface performs effectively. For example, a claustrophobic patient would be more comfortable with a nasal pillow, and a mouth breather or an edentulous patient with air leaks from the mouth would derive appropriate results from either a full face mask or an NIV helmet.

The available NIV circuit also influences the choice of interface. If a single-limb circuit is being used, the mask must have an exhalation port. In the case of intensive care unit ventilators, which have two limbs (one for inspiration and the other for expiration), the masks should not be vented.

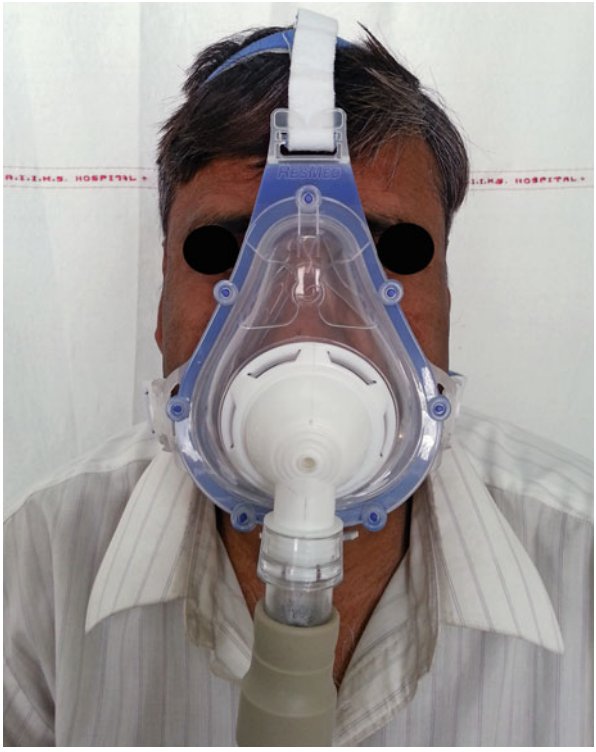

Fig. 3.3 Full-face mask. It is preferred in an acute setting for a patient with mouth breathing

3.4 Use of the Interface Device

Physicians should fully evaluate the patient who is to undergo NIV regarding indications and contraindications to use of the various interfaces. They can then weigh the pros and cons of choosing an appropriate interface. In an acute setting, the health care providers should always have expertise in intensive monitoring of patients on NIV. The patient should be counseled over the basic mechanisms and complications of NIV, after which all the doubts and concerns of the patient must be duly addressed.

After meeting all the above-mentioned conditions, the interface is gently placed over the face of the patient by a physician, who holds it in place while the ventilation is started. When the patient seems comfortable, the straps are

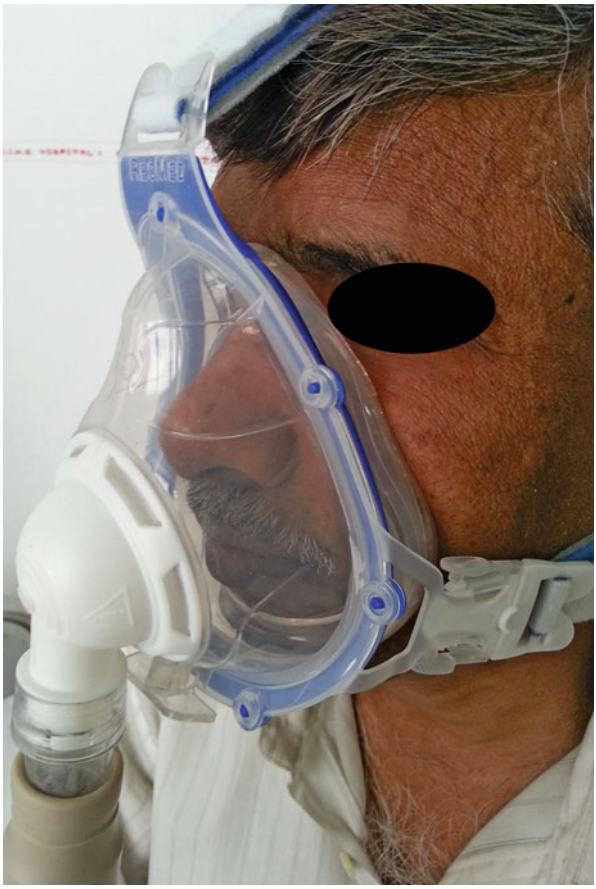

Fig. 3.4 Full-face mask. It is associated with an increased risk of aspiration and makes coughing difficult

tightened adequately to avoid major leaks while always making sure that the patient is experiencing no discomfort. The pressure settings is then titrated upward in small increments to a pressure the patient can tolerate without discomfort and without major leaks. The addition of a heated humidifier helps maintain adequate humidification of the ventilated air, enhancing the patient's comfort.

One should always try to use NIV machines capable of detecting an unintentional air leak while monitoring effective ventilation. These leaks are usually caused by poor fitting of the interface or through the mouth as in the case of the mouth

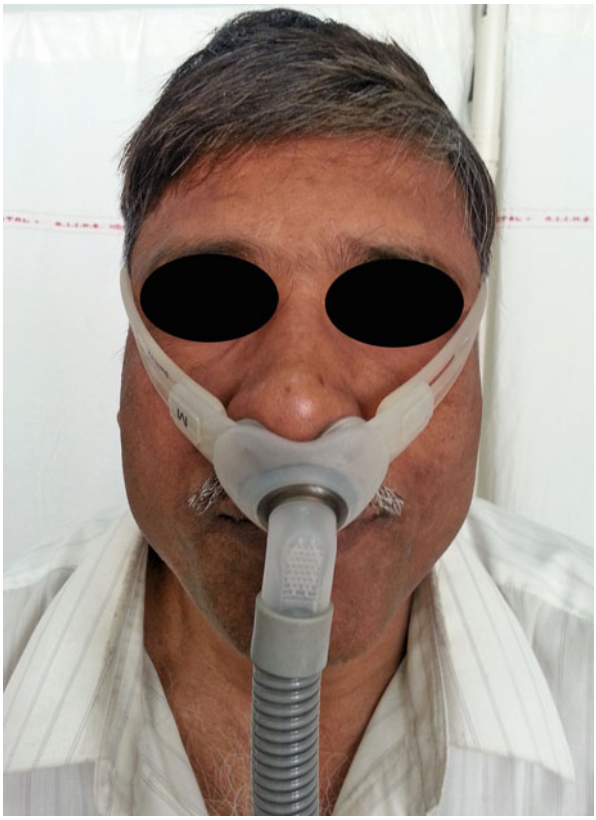

Fig. 3.5 Nasal pillow. It allows speaking, drinking, and coughing. It causes the least claustrophobia

breather using a nasal mask. The ventilator must compensate for the leaks. The intensivist, nursing staff, and trained paramedical staff should monitor the patient carefully, watching for improvement or deterioration of clinical and blood gas parameters. Rapid, appropriate action must be taken in case of impending NIV failure, which could forecast the need for endotracheal intubation or switching to invasive ventilation as a life-saving measure.

The interfaces are not without complications. Thus, the astute clinician must watch carefully for their occurrence while the patient is undergoing NIV. Table 3.2 lists various complications associated with the use of NIV interfaces.

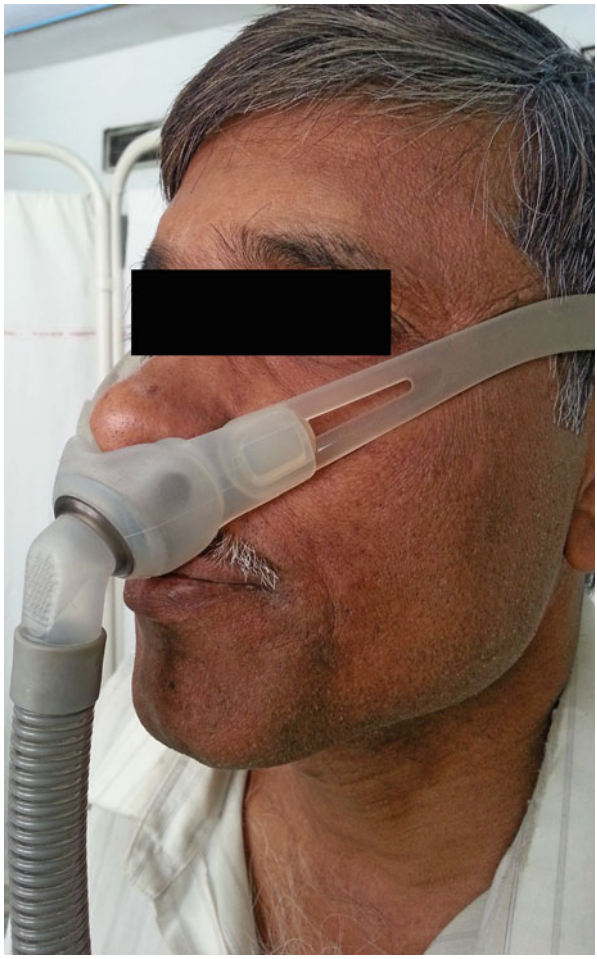

Fig. 3.6 Nasal pillow. It eliminates the risk of redness or pressure sores over the nasal bridge

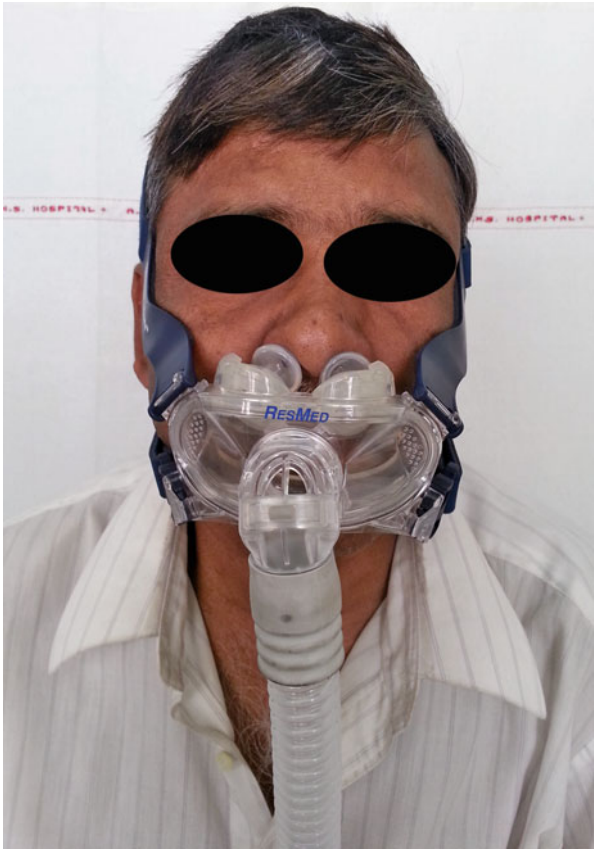

Fig. 3.7 Oronasal mask. Smaller than the full-face mask, it covers only the nose and mouth

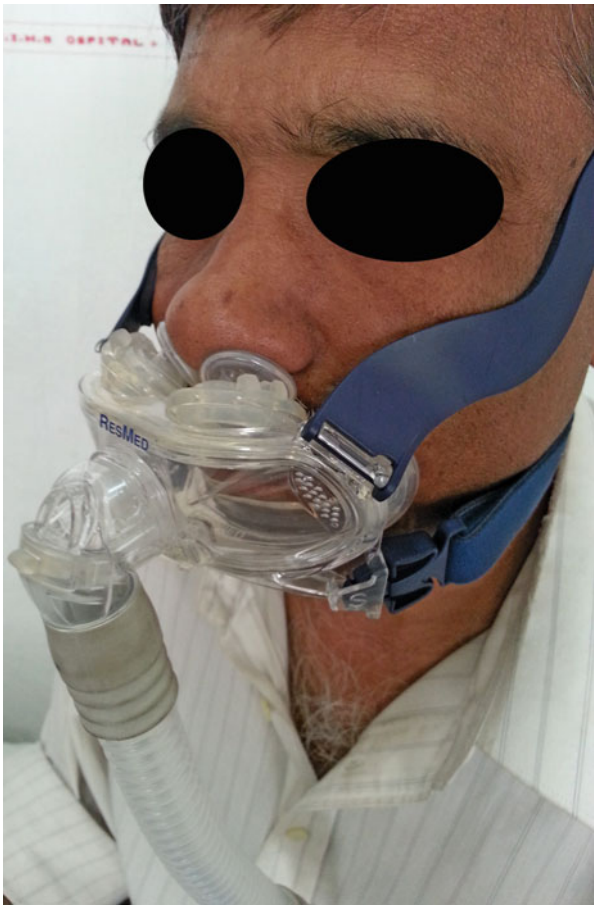

Fig. 3.8 Oronasal mask

Table 3.2 Complications associated with the use of interfaces

Pressure sores and facial pain
Dryness and irritation of eyes, nose, and mouth
Risk of aspiration
Circuit leaks
Claustrophobia
Agitation
Psychological trauma
Increased dead space
Carbon dioxide rebreathing
Patient ventilator asynchrony
Nausea and vomiting
Noise (especially with the NIV helmet [4])

Conclusion

Provision of successful NIV to carefully selected patients requires a proper understanding of the interfaces and their respective advantages and disadvantages. The clinical setting and patient compliance influence the choice of an appropriate interface. Suitable knowledge of the subject is essential. Intense monitoring is required to recognize an early impending NIV failure. Complications associated with an interface also should be recognized early and proper steps taken to address them.

Key Major Recommendations

- Choice of the NIV interface depends upon the clinical scenario, ventilator compatibility, ease of use and durability.
- Nasal mask and nasal pillow are preferred in claustrophobic patients.
- Full face masks are preferred in mouth breathers.
- The fitting of the interface is important to avoid unintentional air leak, at the same time it should be comfortable to the patient.
- Intense monitoring is essential to avoid NIV failure.

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Noninvasive Ventilation Interfaces for High-Risk Infections: Implications for Health Care Workers

4

Raffaele Scala and Arie Soroksky

Keywords
Noninvasive ventilation • Contagious infections • Acute respiratory failure • Health care workers

4.1 Introduction

Respiratory distress due to a wide spectrum of pulmonary infectious diseases—avian influenza (H5N1), varicella, aspergillosis, tuberculosis, and recently severe acute respiratory syndrome (SARS) and swine flu (H1N1)—have been designated "emerging areas" for application of noninvasive ventilation (NIV), which is used to treat patients with acute respiratory failure [1]. Because of the peculiarities of this modality of mechanical ventilation (i.e., intentional and unintentional air leaks), however, theoretical concern has been raised about its use to treat patients with severe pneumonia caused by highly contagious microorganisms. Accordingly, NIV may increase caregivers' exposure to infectious pathogens, leading to potentially disastrous pandemics.

The World Health Organization (WHO) has included NIV among "aerosol-generating procedures" for which the risk of pathogen transmission is possible [2]. However, available data in the literature do not clearly prove the potential NIV-related risks of transmitting contagious diseases from infected patients to health care workers (HCWs).

Fowler et al. [3] examined transmission rates in HCWs caring for SARS patients who required ventilatory assistance. The results showed that physician and nurses

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performing endotracheal intubation were at greater risk of developing SARS [relative risk (RR) 13.29, 95 % confidence interval (CI) 2.99–59.04 %; $p=0.03$]. Even though nurses caring for diseased patients undergoing routine NIV may have been at increased risk of coming in contact with contagious droplets (RR 2.3, 95 % CI 0.25–21.76), this theoretical health-related danger was not translated into a statistically significant clinical event ($p=0.5$). In two studies performed in Hong Kong, there were no cases of SARS in HCWs caring for patients treated by NIV, but the aggressiveness of the surveillance was unclear [4, 5]. Studies from Mexico, Canada, Spain, and Australia reported their experience of treating H1N1 influenza patients with respiratory failure during the recent 2009 swine flu pandemic [2]. A significant proportion of these patients were treated with NIV. There were no reports of disease transmission from noninvasively ventilated patients to HCWs, but these HCWs were not all routinely screened for infection.

More recently, in an elegant experimental setting [6, 7], Hui et al. revealed that the use of various standard face masks for NIV applied to a mannequin was associated with the spread of exhaled air particles—and potentially microorganisms—from patients on NIV within a 1-m distance. According to these experimental studies, respiratory droplet dispersion may be amplified by increased mask leakage and high inspiratory pressure.

Simonds et al. [8] evaluated characteristics of droplet/aerosol dispersion around delivery systems during NIV, oxygen therapy, nebulizer treatment, and chest physiotherapy. They measured droplet size and geographic distribution in three groups of adult patients with chronic lung disease who were admitted to hospital with exacerbation of an infection. Importantly and in contrast with WHO's report, the authors demonstrated that NIV and chest physiotherapy are droplet- (not aerosol-) generating procedures, as they produce droplets >10 μm. Because of their large mass, most of these droplets fall onto local surfaces within 1 m, suggesting that HCWs providing NIV and chest physiotherapy within 1 m of an infected patient should have a high level of respiratory protection. It also suggests that infection control measures designed to limit aerosol spread may have less relevance in regard to these procedures.

In this clinical scenario, technical issues of NIV should be carefully considered. Among them, the type of interface is the "hallmark" of NIV. Differently from invasive ventilation, NIV delivers ventilator support without placement of an artificial airway (i.e., endotracheal or tracheostomy tube). This chapter addresses the implications of the interfaces' features during NIV in patients with a high-risk airborne infection.

4.2 Implications of the Choice of Interface

During NIV, the interface is the key tool that allows interaction between the ventilator and the patient. At the same time, the interface works as a barrier between the patient and the environment. If there is a leak, contamination from the patient's lungs into the environment is unavoidable.

A wide range of interfaces are available to obtain the best fit and comfort for the patient. The choices comprise nasal, oronasal (or full-face), and total-face masks; the helmet; nasal pillows; and mouthpieces. Because of their greater acceptance and

efficacy, oronasal masks are mostly commonly used to deliver NIV in patients with acute respiratory failure. Nasal pillows and mouthpieces are less common choices [9].

Depending on the type of ventilator, the interface may or may not be provided with an exhalation system. Vented masks are used with a single-tube circuit, and nonvented masks are used with double-tube circuit ventilators. In the context of infectious risk owing to dispersion of exhaled air through intentional air-leak systems, theoretically vented interfaces are associated with greater risk of spreading infected air particles than nonvented interfaces. Among the vented masks, those provided with an expiratory port (i.e., whisper swivel) in the circuit allow more diffuse air leakage than those with an exhalation system built inside the mask [10].

Theoretically, full-face masks might be preferred to nasal masks to prevent the potential spread of contaminated exhaled air particles from unintended air leaks through the mouth (Fig. 4.1). With this perspective, the choice of the brand and size that best fits the anatomy of the patient's facial profile and allows delivery of adequate pressure is crucial to minimizing unintended air leaks around the interface. There are no data, however, to confirm that this theoretical strategy would have a positive impact under clinical conditions.

The helmet is a new interface for delivering NIV. It surrounds the head and neck of the patient. Once the helmet is pressurized, a soft collar gently adheres to the patient's neck and shoulders, providing a greater and more tolerated seal than standard face masks [10]. Within certain limits, the higher the pressure is inside the helmet, the better is the seal. It follows, then, that with small leaks there is less dispersion of expired gas by the patient. This is particularly useful in patients suffering from hypoxemic acute respiratory failure, which requires high levels of positive end-expiratory pressure (PEEP) and peak pressure. In contrast to use of the helmet, the application of high ventilation pressures during NIV with a face mask may tear off the patient's skin surface, thereby increasing leaks and the amount of potentially infected exhaled air. Furthermore, most patients better tolerate the helmet and for longer times than they do face masks [10]. Thus, the helmet allows prolonged applications with fewer interruptions. It is important to note that generally the acutely hypoxemic patient poorly tolerates disconnection from an NIV device. Disconnection also presents a potential risk for transmission of high-risk infections to caregivers. It is speculated, but not yet proved, that use of the helmet (when available) for NIV, together with negative-pressure rooms equipped with high-efficiency particulate air (HEPA) filters, may decrease dispersion of infected respiratory droplets.

4.3 Implications for Caretaker Behavior

Only a few reports of infectious disease transmission with NIV therapy have been published. Nevertheless, reasonable and adequate precautionary steps should be taken to protect health care personnel as well as other patients and family members [2].

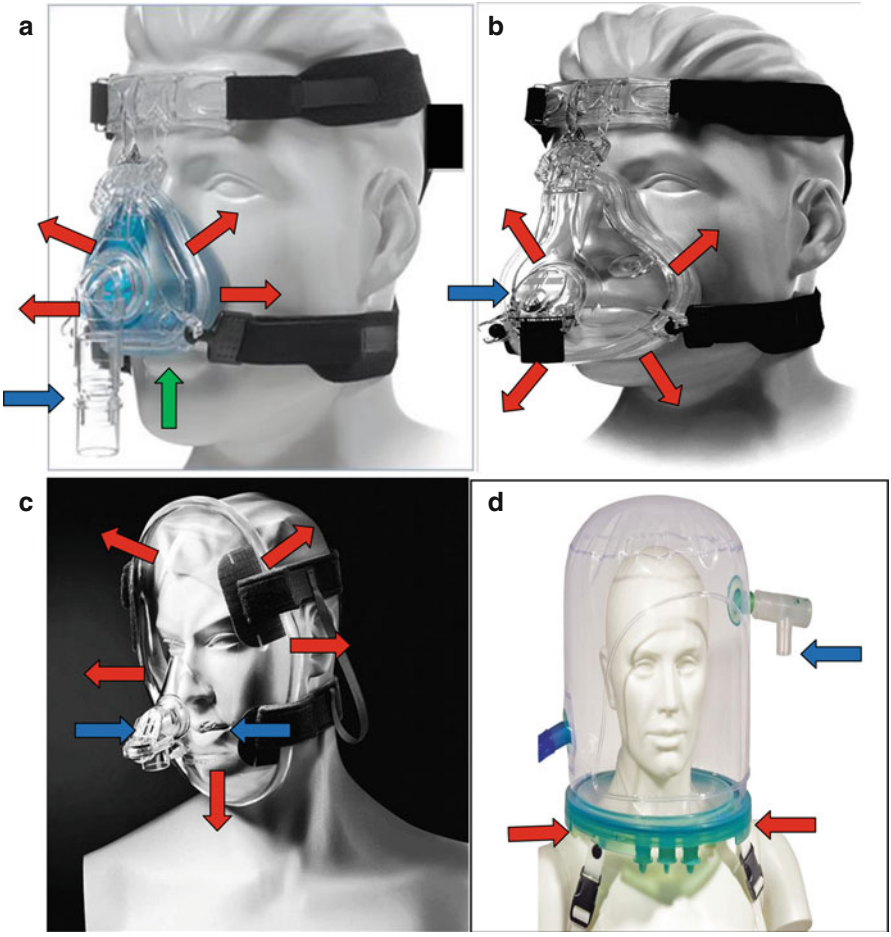

Fig. 4.1 Details of unintentional leaks [between the interface and the patient's face (*red arrows*) and throughout the mouth (*green-red*)] and intentional leaks [throughout the expiratory port (*blue arrows*)] in a patient undergoing noninvasive ventilation (NIV) delivered by a single-tube ventilator with a nasal mask (**a**), full-face mask (**b**), total-face mask (**c**), or helmet (**d**)

Above of all, HCWs should be aware of the potential risks of caring for potentially contagious patients during NIV application and should take the appropriate precautions suggested by the recommendations for contagious diseases (Table 4.1). HCWs must use personal protective equipment complemented by strict hand hygiene before and after entering the room and after managing the patient.

The HCWs should pay special attention during the phases of disconnecting the patient from the NIV. It is advisable to switch the ventilators off quickly, as soon as the circuit is taken away from the mask. Such action helps prevent dispersion of the substantially large expiratory flow near the HCWs. This is also true during the

Table 4.1 Health care workers' precautions around patients suspected of being infectious who are being treated with noninvasive ventilation

Health care personnel should use full protective clothing as for all aerosol-generating procedures: an FFP3 mask when available (N95 masks are the second choice), eye protection, gown, gloves, and apron. Patients should be managed in negative-pressure rooms equipped with HEPA filters (where available) and with anterooms. Preferred interface is the helmet, if applicable and available. If not, a nonvented full-face mask may be used
Viral/bacterial filter (99.9997 efficiency) should be used between the mask and the interface and the expiratory port and at the outlet of the ventilator
Ventilators with double-hose tubing (inspiratory and expiratory limbs) may be advantageous
Lowest possible pressures (e.g., EPAP 5, IPAP < 10 cmH_2O) are titrated to the respiratory rate and arterial blood gas tensions. When applying a helmet, inspiratory pressures may be at least twice the pressures used with standard face masks
Apply and secure the mask before turning on the ventilator
Turn off the ventilator before removing the mask

EPAP expiratory positive airway pressure, *HEPA* high-efficiency particulate air, *IPAP* inspiratory positive airway pressure

maneuvers required to deliver bronchodilators during NIV. To decrease the need for NIV disconnections, it is advisable to pay attention when selecting the device to ensure that it is the one that would be best tolerated by the particular patient. Light continuous analgesia and sedation can be considered in expert high-intensity-care settings [1].

Conclusions

Despite the lack of robust clinical data regarding transmission of potentially contagious infections via NIV from patients to HCWs, general prophylactic strategies and recommendations on technical issues should be implemented. Safety can be achieved if the NIV teams who manage patients with suspected or proven acute respiratory failure caused by a contagious disease establish and follow protocols designed to address these issues.

Key Major Recommendations

- NIV is a droplet-generating, not an aerosol-generating, device.
- NIV may be associated with a theoretical risk of transmitting infected exhaled particles to HCWs within 1 m of the interface.
- In terms of the risk of transmitting contagious diseases during NIV, nonvented interfaces are preferred to vented interfaces, oronasal are preferred to nasal interfaces, and the helmet interface is preferred to other interfaces.
- Minimum inspiratory and expiratory pressures that are able to meet the patient's ventilator demand should be set during NIV.
- Patient's disconnection from the NIV should be reduced as much as possible.

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Heated Humidifier

5

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Keywords
Heated humidifier • Infections • Noninvasive mechanical ventilation

5.1 Introduction

During nasal respiration, the inspired air is warmed and humidified by evaporation of water from the surfaces of the mucous membranes. The air in the pulmonary periphery thus becomes saturated with water vapor. The point at which gases reach 37 °C and 100 % relative humidity (corresponding to an absolute humidity of 44 mg/L) is called the "isothermic saturation boundary" (ISB). The ISB is located well below the carina during quiet breathing. The evaporation leads to loss of energy, which results in cooling of the mucous membranes. This fall in temperature allows recovery of water and heat through condensation during the subsequent expiration. Delivery of cool, dry gases to the patient with a bypassed upper airway can have dire consequences, including alterations in tracheobronchial structure and function. Common findings include inspissation of secretions, airways plugged with mucus, ciliary dyskinesis, epithelial desquamation, and tracheal tube occlusion [1]. For intubated patients in whom the upper airway is bypassed—which otherwise would have supplied 75 % of the heat and moisture to the lower respiratory tract—a heated humidifier can supply the same.

Humidification of respired gases during mechanical ventilation is the standard of care and should be started as early as possible. It should not be discontinued even during short-term postoperative mechanical ventilation, patient transport, or emergency room situations. Two systems are commonly used to humidify and

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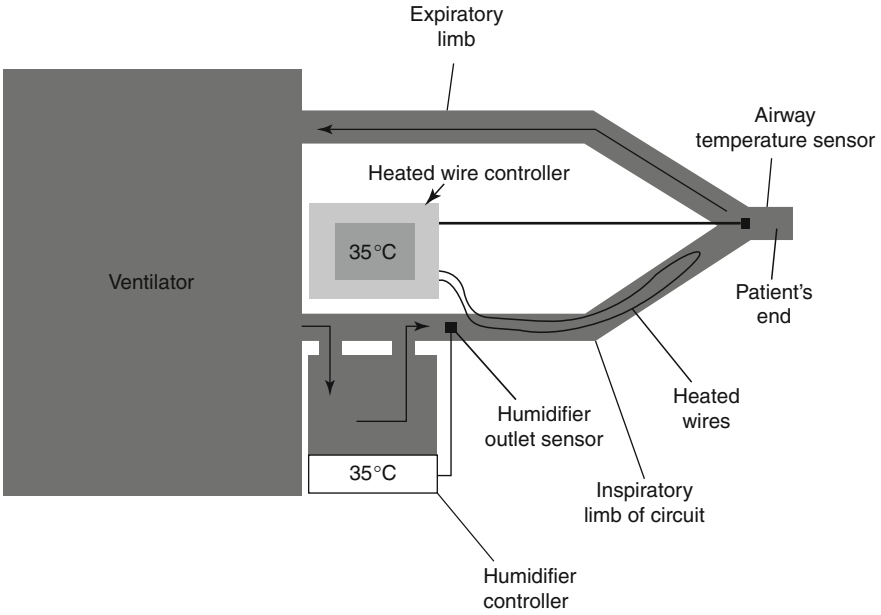

Fig. 5.1 Heated humidifier system. The temperature is kept constant throughout the inspiratory limb of the circuit by a dual sensor system [5]

warm inspired gases: heated humidifiers (HHs) and heat and moisture exchangers (HMEs), also called "artificial noses." This chapter discusses HHs. Refer to Chap, 4 for details on HMEs.

5.2 Device Description

The HH is an active humidifier that adds water vapor and heat to the inspiratory air from temperature-regulated water reservoirs independent of the patient. The humidifiers are usually connected to the inspiratory end of the breathing circuits. They are often controlled by a microprocessor, which monitors the readings from various sensors and makes the necessary adjustments for maintaining set humidity and temperature. If one or more parameters are out of range, the microprocessor sends a signal to activate an audible or visual alarm. The respiratory gas is warmed inside the humidification chamber to a set target temperature, which is achieved by an additional heating device. The warmed gas is then humidified by addition of water vapor from the heated water reservoir. The larger the area of contact between water and gas, the more opportunity there is for evaporation to occur. Inspiratory circuit tubing containing a heated wire is then used to maintain or slightly raise the gas temperature before it reaches the patient. This helps prevent water rain-out in the circuit and a consequent fall in the gas temperature, although it can decrease the relative humidity of the delivered gas.

An HH system is depicted in Fig. 5.1. Various methods can be used to evaporate water in HHs and are discussed later in the chapter.

5.2.1 Cascade Humidifiers

With the cascade humidifier, the flow is passed underneath the surface of the water in a heated water reservoir. It is, in principle, a bubble-through humidifier (Fig. 5.2) that utilizes the bubble-diffusion technique: A stream of gas is directed underwater, where it is broken up into small bubbles. As the gas bubbles rise to the surface, evaporation increases the water vapor content within the bubble. The smaller the bubble, the greater is the water/air surface area ratio. A sintered filter can be used to reduce the bubble size and hence increase the surface area for evaporation (Fig. 5.2). Spraying water particles into the gas is an alternative to dispersing gas bubbles in water. It is accomplished by generating an aerosol in the gas stream. The water content of the inspired air can be adjusted by varying the temperature of the water in the reservoir. The cascade humidifier exhibits the highest measured inspiratory flow resistance. Therefore, it cannot be recommended for use with intubated and spontaneously breathing patients.

5.2.2 Passover Humidifiers

With the passover humidifier, the airflow is directed over a water surface. These humidifiers offer several advantages over bubble humidifiers. First, the inspiratory air does not need to be passed underneath the water surface of the reservoir. Airway resistance is reduced compared with that of cascade humidifiers. Second, unlike bubble devices, the passover humidifiers can maintain saturation at high flow rates. Lastly, they do not generate any aerosols and thus pose minimal risk of spreading infection. There are three common types of passover humidifiers.

First, the simple reservoir-type humidifier directs gas over the surface of a volume of heated water. The surface of the gas–fluid interface is limited, however.

Second, in wick humidifiers (Fig. 5.2) the accessible surface area is increased by means of a wick made of water-absorbent blotting paper. The wick is placed upright, with the gravity-dependent end in a water reservoir and surrounded by a heating element. The water is continually drawn up from the reservoir by means of capillary action and keeps the wick saturated. The dry gas entering the chamber flows around the wick, picks up heat and humidity, and leaves the chamber fully saturated with water vapor.

The third type is a membrane-type humidifier (Fig. 5.3). It separates water from the gas stream by means of a hydrophobic membrane. Water vapors can pass easily through this membrane, but liquid water and hence the pathogens cannot.

5.3 Requirements for a Humidification Device

5.3.1 Operating Range

The device must ensure physiologic conditions in the respiratory tract and avoid pulmonary water losses of >7 mg/L, which are due to ventilation with dry gases. Most humidifiers have humidity settings from 0 to 100 %. Ventilation with

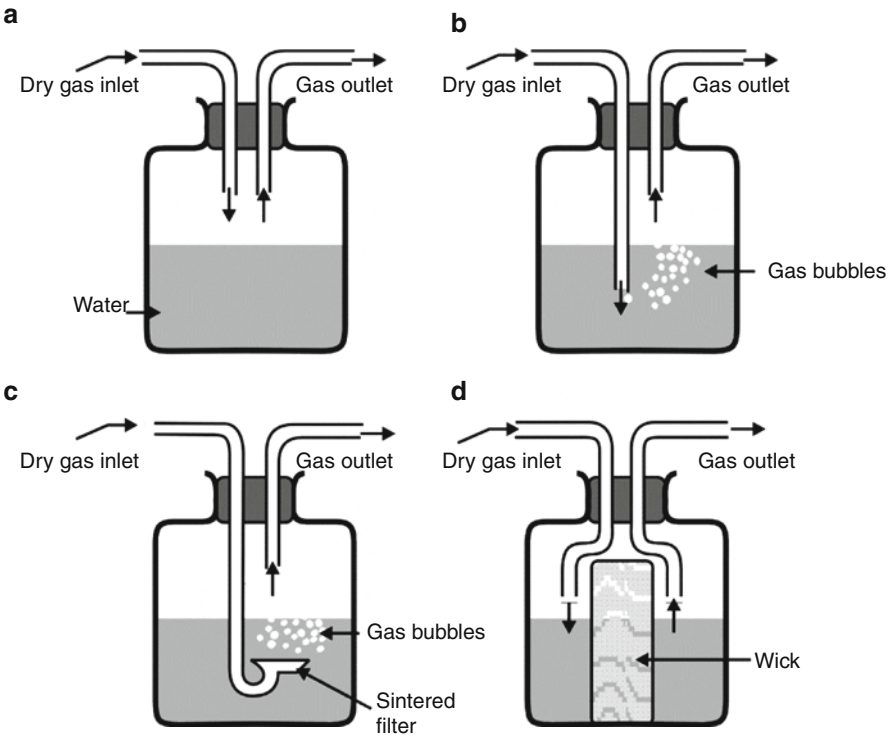

Fig. 5.2 (**a**) Simple bottle humidifier. (**b**) Bubble-through humidifier. (**c**) Bubble-through humidifier with sintered filter. (**d**) Wick humidifier [6]

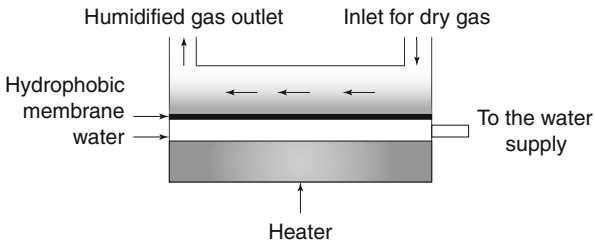

Fig. 5.3 Membrane-type heated humidifier [5]

oversaturated gases should also be avoided. The recommended temperature of inspired gas in an intubated patient is ≥34 °C but <41 °C at the circuit Y-piece. The recommendation for moisture is a minimum of 33 mg/L. The humidifier's heating unit should shut itself off automatically at temperatures above 41 °C to avoid heat damage to the trachea.

These devices influence the inspiratory and expiratory resistance and the functional dead space in different ways. This is especially important in spontaneously

breathing patients to avoid additional work of breathing and hypercapnia. Resistance values for defined flows may be obtained by referring to the International Organization for Standardization (ISO) 8185:1997 for HHs. The inspiratory flow resistances of most HHs range between 0.5 and 1.5 hPa/L/s [2].

5.3.2 Safety Features

The device should have the means to prevent any possible adverse effects on the patient and the operator. For example, the humidifiers should have a high- and low-temperature alarm and one that alerts the operator to a faulty sensor connection, among others. They should also have shut-down mechanisms that turn the humidifier or parts of it off to ensure patient safety. For example, the power to the heating filament should be turned off if the safe temperature is exceeded. The device should also have a fuse or circuit breaker for protection against power surges. Proper grounding of the device must be ensured.

5.3.3 Common Concerns with the Use of HHs

Most users do not know the function of the humidity correction control knob that is on some devices. This carries a high risk of an incorrect setting, which in turn can lead to insufficient humidification. There is insufficient knowledge among critical care physicians with regard to the optimal inspiratory gas temperature. A permanent default temperature setting of 37 °C can simplify this situation and simultaneously increase patient safety. In any case, there is no clinical need for reducing or elevating the temperature to a level higher than body temperature. Faulty operation is another area of concern. For example, some devices do not have an alarm if the operation is started without the proper amount of water.

5.4 Clinical Decision Making for the Use of Humidification Under Specific Conditions

Selection of the device to be used on a given patient should be based on the patient's underlying lung disease, ventilator settings, intended duration of use, presence of leaks, and body temperature, among others [1]. An algorithm for selection of humidification devices in an adult intensive care unit (ICU) is presented in Fig. 5.4.

5.4.1 Acute Respiratory Distress Syndrome

A significant improvement in $PaCO_2$ is associated with switching to an HH from an HME in patients who have acute respiratory distress syndrome (ARDS) [3].

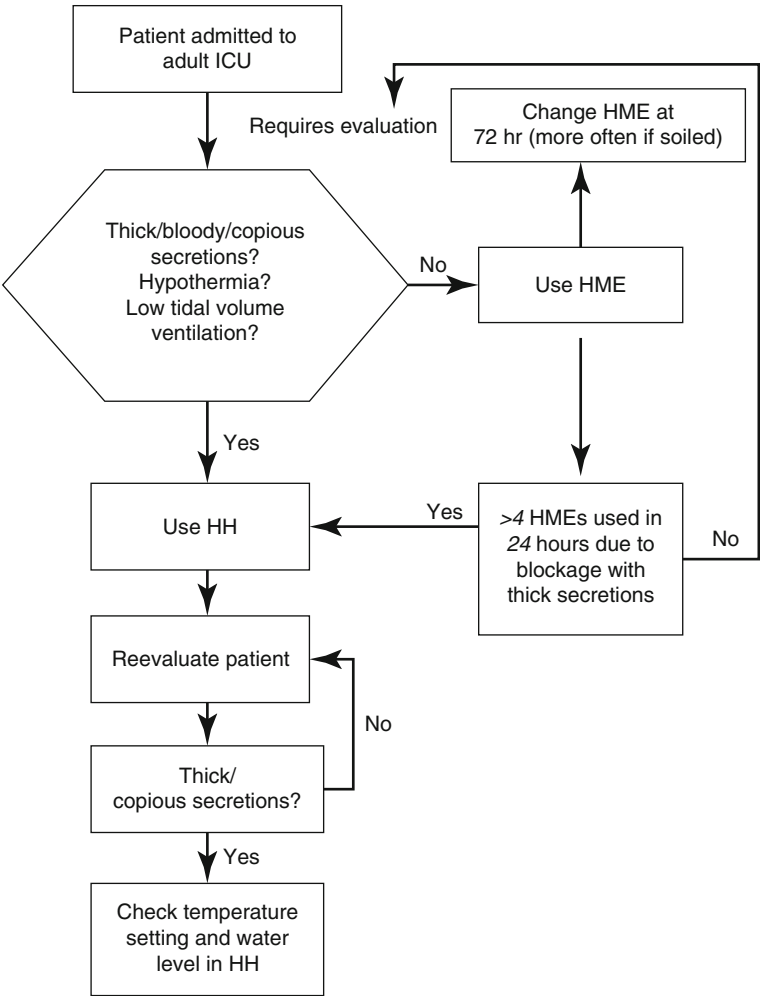

Fig. 5.4 Algorithm for selecting humidification devices in an adult intensive care unit. Thick secretions refer to secretions that remain stuck to the walls of the suction catheter after it is rinsed with saline during two consecutive suctioning procedures. Bloody secretions refer to hemoptysis, which is more than small streaking. Copious secretions, as seen in those with pulmonary edema or pneumonia, may occlude the medium. Low tidal volume ventilation refers to ventilation with a tidal volume ≤6 mL/kg predicted body weight [1]

Compensation for HME dead space is possible by increasing the set tidal volume. This compensation, however, increases peak airway pressure and the mean airway pressure, which may not be acceptable in ARDS patients [1]. Therefore, if low-tidal-volume ventilation is used, as in the case of ARDS and hypercapnia, an HH is the humidification system of choice.

5.4.2 Weaning from Mechanical Ventilation

During spontaneous-breathing trials, the use of an HME (with dead space of 100 mL) results in increased ventilator requirement and an increase in the work of breathing compared with HH. The use of an HME results in higher $PaCO_2$ despite attempts by patients to compensate by increasing their minute ventilation [4]. Thus, an HH should be used for weaning, including spontaneous-breathing trials.

5.4.3 Humidification During Noninvasive Ventilation

The high flows delivered during noninvasive ventilation (NIV) quickly result in oral and nasal dryness, which can proceed over time to mucosal cracking, bleeding, and pain. Addition of humidity seems to reduce symptoms of airway dryness. The use of an HME during NIV is not advisable for two reasons. First, the leaks around the mask and built-in leaks for CO_2 clearance prevent the movement of expired gas through the HME, thereby causing ineffective function of the HME. Second, the HME adds to dead space and may reduce the effectiveness of NIV [1]. Therefore, humidification during NIV should be accomplished with an HH.

5.4.4 Hypothermia

Patients who are hypothermic are often treated with superheated inspiratory gases. This practice has no scientific basis. Although heating gases to 44 °C seems to have few acute adverse effects, it seems to be of little use in humans [1]. Attempts at whole-body rewarming through the respiratory tract are not supported by the literature.

5.4.5 Very-Low-Birth-Weight Infants

The safety and efficacy of HME for very-low-birth-weight infants have not been established conclusively. Thus, an HH should be used in these infants.

5.5 Potential Complications with Use of an HH

The complications associated with using an HH have been addressed in the literature [1, 7].

- *Electrical shock*: There is a risk of electrical shock to both the patient and the operator if the device is not properly grounded.
- *Burning the patient's airway*: There is a risk of burning the patient's airway with the use of an HH if excessive heat is introduced. Low humidity and high airflow can also contribute to this situation.

- *Water entering the breathing circuit*: Some humidifiers have an elevated water supply source. In these humidifiers, water flows down from the water supply to the heating chamber to be evaporated. If the amount of water supplied is more than the evaporation rate, sufficient water can enter the breathing circuit and can limit the air passage.
- *Bacterial colonization of respiratory tubing and ventilator-associated pneumonia (VAP)*: Although HHs do not influence the occurrence of VAP, they are associated with rapid bacterial colonization of the respiratory tubing. This bears the potential for cross-contamination especially when the circuit is disconnected from the patient and the colonized condensate is aerosolized. Condensate from the patient circuit, which is infectious waste, should never be drained back into the humidifier reservoir. Strict universal precautions should be employed during its disposal. High-level disinfection is of paramount importance for reusable HHs.
- *Care provider burns*: There is a potential that care providers can be burned by the hot metal of HHs.
- *Hypothermia and hyperthermia*: These conditions can occur if the range of the temperature supplied is not within the recommended range.
- *Under-humidification and impact of mucus secretions*: There is a risk of airways becoming plugged with mucus because of under-humidification, which can lead to increased resistive work of breathing, hypoventilation, and/or trapped alveolar gas. Mucus plugs can result from low relative humidity of the delivered gases, which might be due to an inappropriate setting or a low water level in the humidifier.
- *Pooled condensate in the patient circuit*: Condensate can pool in the patient's circuit, leading to inadvertent tracheal lavage, elevated airway pressures, patient–ventilator dysynchrony, and/or improper ventilator performance. The amount of condensate is an indicator of adequate performance of the humidifier except when the reliability is compromised by variations in the ambient temperature, especially a high temperature.

5.6 Contraindications, Precautions, Warnings

There are no contraindications to the use of an HH [1].

The critical care team should be aware of the warnings and precautions pertaining to the use of an HH (Table 5.1). Trained individuals with sufficient knowledge to evaluate humidification are essential for appropriate usage and maintenance of the HH.

5.7 Active HMEs

"Active" HMEs combine an HME with an integrated HH. Their use can cause problems because of their complexity. They are indicated in patients with large-tidal-volume (>1 L) ventilation and those with a lung fistula where portions of the exhaled gas are lost.

Table 5.1 Precautions and warnings pertaining to a heated humidifier

Precautions	Warnings
When mounting a humidifier, always ensure that the humidifier is positioned lower than the patient	Do not fill the chamber above the maximum level as liquid could enter the breathing circuit if the chamber is overfilled
Water traps should be arranged at the lowest point of the circuit so the condensate drains away from the patient	Never drain the condensate back into the humidifier reservoir as it is considered infectious waste
Humidification device should be inspected with every ventilator system check and condensate removed from the circuit	Never use a device for patient care that fails to perform according to the manufacturer's specifications

Key Major Recommendations

- The heated humidifier is an active humidifier that adds water vapor and heat to the inspiratory air independently of the patient.
- Passover humidifiers offer several advantages over bubble humidifiers. An HH is preferred over an HME in patients with ARDS, during NIV, during weaning from mechanical ventilation, in very-low-birth-weight infants, and in patients in whom HME is contraindicated.
- Common problems with HH include condensation, cross-contamination, burning the patient's airway, and ensuring proper conditioning of the inspired gas.
- A temperature alarm, automatic shut-down mechanisms, and sometimes a permanent default temperature setting of 37 °C can help increase patient safety.

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Preventing the Spread of Aerosol Infection During Application of High-Frequency Jet Ventilation by Mask

6

Viliam Donic, Pavol Torok, and Zoltan Tomori

Keywords
HFJV • Protective lung ventilation • NIV • High-risk infections and mass casualty events

6.1 Introduction

High-frequency jet ventilation by mask (HFJV-M) is another form of noninvasive ventilation (NIV) and a new approach to improving patient–ventilator synchronization during NIV. This method uses a supraphysiological frequency of 120 breaths/min, which does not interfere with the patient's spontaneous breathing. Lung receptors are not able to respond because they are not stimulated by this frequency. HFJV-M does not provoke cough, nor does the patient fight the ventilator.

The ventilator (Paravent; Kalas Medical Ltd., Slovakia) uses a special patented pressure generator with an open central receiving channel [1]. The machine is commercially available and represents a breakthrough in NIV. It addresses almost all major disadvantages or concerns regarding NIV in patients with a high-risk infection and is advantageous in other situations. There are several reasons for its usefulness: Its construction and principle are simple, and it is not expensive. The ventilator does not require synchronization with the patient, who is simply connected with the ventilator by a naso-oral nonvented mask. No other signal from the patient, catheter, or nasal tubing is necessary. The ventilation circuit is sealed, and a nonvented orofacial mask is connected to a specially designed pressure generator. The system is open to the atmosphere only during inspiration. The patient can breathe spontaneously or switch over to being completely dependent on the ventilator if necessary,

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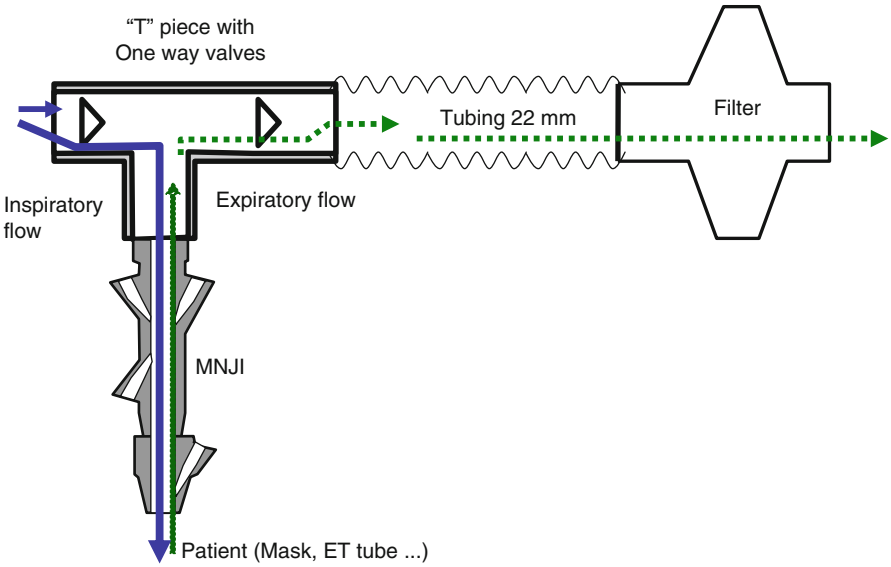

Fig. 6.1 To prevent airborne infection spread, it is necessary during HFJV-M or any other HFJV application to use an expulsion set. It is connected to a pressure generator (MNJI), and the expiratory flow is directed through an appropriate bacterial/viral filter to prevent contamination of the environment by expired infected aerosol droplets

without interruption or use of any trigger. The exhaled air passed through a high-efficiency particulate air (HEPA) filter, where the aerosol is condensed and infection agents are trapped (Fig. 6.1). The system can be used even during a bioterrorist attack because its ventilation is effective in an atmosphere of toxic gases or bacterial contamination. One of the advantages of this method is that it performs protective lung ventilation with a significant reduction in ventilator-induced lung injury because of its principle. Only very low volumes and low insufflation pressure pulses are used. Nevertheless, the patient's laboring to breathe is significantly alleviated because of the decreased volume of dead space ventilation. Also, HFJV-M has minimal impact on venous return and the patient's hemodynamics because there are almost no intrathoracic pressure changes, unlike that with continuous positive airway pressure (CPAP) or bilevel positive airway pressure [2–4]. The breathing effort during expiration is also significantly reduced. Alveolar recruitment is achieved because positive alveolar pressure is present during the whole respiratory cycle. These advantages improve gas exchange and oxygenation, and adequate CO_2 removal is ensured. Improvement is significantly better than that with CPAP or other NIV applications.

The method is physically safe and is not subject to barotrauma, even in cases when the lungs are severely damaged by pathological processes. One ventilator with an appropriately selected pressure generator and mask can be used for ventilation of both neonates and adults. These advantages make HFJV-M an outstanding method for NIV, and it can be seriously considered for worldwide use. There are

many medical applications of this method in addition to NIV. Several HFJV and HFJV-M methods can be found in the literature [5–7].

6.2 Preventing Spread of Aerosol Infection During HFJV (Including HFJV-M)

The expulsion set consists of a T-piece, which is connected to the proximal end of the central channel of the pressure generator (multi nozzle jet injector (MNJI)). The T-piece is equipped internally with two one-way valves that direct gas passage. During inhalation the surrounding air from the atmosphere reaches the central channel, and during exhalation the gas goes through a bacterial filter and then into the atmosphere. T-pieces with integrated one-way valves are connected with the bacterial filter by a hose (diameter 22 mm, maximum length 200 cm). The expulsion set is part of HFJV PARAVENT ventilators and is meant for one-time use only. The infected aerosol present in exhaled gas partially condenses inside the hose, and the rest is trapped inside the HEPA filter.

Key Major Recommendation

- This method is physicaly safe and is not object to barotrauma. Therefore it is particularly recomended in cases when the lungs are severely damaged for instance by toxic gases inhalation, a virus infections, or in pulmonary oedema of various origines.

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Part II

Clinical Indications in Adults

Noninvasive Mechanical Ventilation for Hypoxemic Respiratory Failure-Related Infectious Diseases

7

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Keywords
Noninvasive mechanical ventilation • Acute hypoxemic respiratory failure • Community-acquired pneumonia

7.1 Introduction

The strict range of applicability of noninvasive ventilation (NIV)—which had been applied only to patients with an exacerbation of chronic obstructive pulmonary disease (COPD) or acute cardiogenic pulmonary edema (ACPO)—has been extended during the last two decades.

Although with different levels of evidence [1], the practice of NIV has produced several studies that support its use in diverse situations of respiratory failure to improve oxygenation and relieve dyspnea. It also is used to avoid endotracheal intubation (ETI) and its resulting complications, such as infections associated with invasive mechanical ventilation (IMV), increased risk of death, prolonged hospital stay, and economic cost. Thus, NIV has been used under the following conditions.

- Evidence level 1—derived from systematic reviews with randomized homogeneity-controlled trials (RCTs) and individual controlled trials with a narrow confidence gap. Here, NIV is used to treat COPD exacerbations or ACPO, to facilitate weaning/extubation from IMV in patients with COPD, and for acute respiratory failure (ARF) of immunocompromised patients.

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- Evidence level 2—derived from systematic reviews with homogeneity of cohort studies, individual cohorts, and/or poor-quality RCTs. NIV is applied in patients with a "do not intubate" order, as a palliative measure in terminally ill patients, to prevent extubation failure in patients with COPD or heart failure, for community-acquired pneumonia (CAP) in COPD patients, to prevent and treat postoperative respiratory failure, and to prevent ARF due to asthma. Also in this category, but with greater caution and according to the case, NIV may be indicated for severe CAP and for preventing extubation failure in patients without COPD.
- Evidence level 3—derived from systematic reviews with homogeneity of case–control studies and an individual case–control study. NIV is suggested for neuromuscular diseases and kyphoscoliosis, partial obstruction of the upper airway, thoracic trauma, and treatment of ARF in patients with asthma. With more caution and strict surveillance, NIV may also be indicated for acute lung injury and acute respiratory distress syndrome (ARDS).
- Evidence level 4—derived from case series and poor-quality cohort and case–control studies. NIV is suggested for obesity-related hypoventilation, cystic fibrosis, and in the elderly (>75 years) with ARF. With greater caution and according to the case, it is also indicated for idiopathic pulmonary fibrosis.

7.2 Analysis

Numerous RCTs have focused on NIV during the last decade. The studies, however, have reported conflicting evidence regarding any permanent benefit for patients with acute hypoxemic respiratory failure (AHRF). These conflicts probably arise because most of these studies are small, have many differences among them, and the success of NIV varies according to the cause of hypoxemic respiratory failure.

For example, in the 2006 meta-analysis of Keenan et al. [2], which included eight RCTs that had studied patients with AHRF secondary to causes other than ACPO, the NIV reduced the ETI rate by 23 %, the length of stay in the intensive care unit (ICU) by 2 days, and ICU mortality by 17 % (absolute risk reduction). In contrast, in a 2008 observational study by Schettino et al. [3] that included 449 patients, of whom 144 underwent NIV for AHRF, unfavorable results were obtained. These authors found that 60 % of this population were in need of ETI, and the hospital mortality rate was 64 %.

In 1996, Meduri et al. [4] were among the first to show the potential of NIV for preventing ETI specifically in patients with AHRF secondary to community-acquired pneumonia (CAP). However, the sample was very small: Only 14 patients had CAP, and among them only 7 had hypoxemic failure. The observational study comprised 158 patients, 41 of whom had hypoxemia and 74 had hypercapnia. The results of this study showed the same percentage of ETI requirement (34 %) in patients with hypoxemic failure as in those with hypercapnia. The mortality rate among those requiring ETI was higher in the group with AHRF (34 % vs. 20 %).

In 1999, Confalonieri et al. [5] demonstrated the effectiveness and safety of NIV in a prospective, controlled trial that included 56 patients admitted to the ICU. The authors showed that NIV was well tolerated and, relative to the control group

(who underwent conventional medical treatment), provided a significant reduction in the respiratory rate and the number of patients who required ETI (21 % vs. 50 %, $p=0.03$), and it shortened the ICU stay (1.8 vs. 6.0 days, $p=0.04$). There were no statistically significant differences in the two groups regarding hospital mortality or survival rates after 2 months of follow-up. Moreover, at 2 months there was a reduced workload for the nursing staff and improved survival among patients with COPD who were treated with NIV (88.9 % vs. 37.5 %, $p=0.05$).

In 2001, Jolliet et al. [6] reported on 24 patients with severe pneumonia (the criterion for which was an average PaO_2/FiO_2 of 104 mmHg) but no history of chronic lung disease. The authors showed a high ETI rate (66 %) despite NIV. The positive aspects were the initial improvement in arterial oxygenation, shorter hospital stay, and no overworked nursing staff.

That same year, Antonelli et al. [7] presented a prospective multicenter study on predictors of NIV failure in 350 patients with AHRF. NIV had a failure rate of 30 %. The ETI was especially high when AHRF was due to CAP (50 %) or ARDS (51 %).

In 2002, Domenighetti et al. [8], in a prospective observational study, compared the efficacy of NIV in patients without COPD but with hypoxemic respiratory failure due to ACPO (15 patients) or severe CAP (18 patients). One patient (6.6 %) with ACPO and seven (38 %) in the group with severe CAP were intubated ($p=0.04$). The mortality rate was higher in the CAP group (28.0 % vs. 6.6 %, $p=0.2$).

In another prospective RCT conducted in three ICUs, Ferrer et al. [9] selected 105 patients with AHRF, including 51 given NIV and 54 with conventional oxygen therapy. The ETI rate in the 34 patients with severe AHRF due to CAP who received NIV was 26.3 % compared to 73.3 % in the control group ($p=0.017$). Based on a multivariate analysis, the authors concluded that NIV functioned as an independent factor in reducing the risk of ETI and mortality at 90 days. They suggested that NIV was a first-line intervention in patients with severe AHRF in the absence of contraindications to using it.

In 2010, Cosentini et al. [10] evaluated the effectiveness of continuous positive airway pressure (CPAP) administered by helmet in patients with moderate AHRF (PaO_2/FiO_2 210–285) secondary to CAP. This multicenter, prospective RCT examined 47 patients (37 without COPD) and concluded that CPAP by helmet provides faster oxygenation ($PaO_2/FiO_2>315$) in a larger number of patients with AHRF due to CAP than in those who were given conventional oxygen therapy.

In 2012, Carrillo et al. [11] examined the effectiveness of NIV in 184 patients with severe respiratory failure due to CAP. Among them, 102 were classified as having "de novo" inadequate breathing, and 82 had previously been diagnosed with heart or respiratory disease. All patients were given NIV. Those with de novo respiratory failure had a higher failure rate than the patients with a history of heart or respiratory disease (46 % vs 26 %, $p=0.007$).

7.2.1 Immunosuppression

Another important population in which the ventilation strategy with NIV has been attempted comprises immunosuppressed patients with pulmonary infiltrates and

ARF. They are especially vulnerable because their rate of morbidity secondary to ETI is high (up to 70 % depending on the series). Most of the studies conducted in this population have been observational and/or retrospective. We point out two studies that are prospective RCTs.

In 2000, Antonnelli et al. [12] studied 40 immunosuppressed patients after solid organ transplant. Half of the patients ($n=20$) were treated with NIV and the other half ($n=20$) with oxygen. Overall, 10 % of the 40 patients had AHRF secondary to pneumonia and were assigned in equal numbers to the two groups. The ETI and mortality rates in the AHRF subgroups with pneumonia were the same, although, in this randomized trial, NIV significantly reduced the all ETI requirement rates, the number of fatal and septic complications, and mortality in the ICU.

In 2001, Hilbert et al. [13] examined 52 immunosuppressed patients with pulmonary infiltrates, fever, and AHRF. In all, 28 % of the patients had hematological malignancies and neutropenia. One group of patients ($n=26$) underwent NIV intermittently, and the other group was treated with conventional oxygen therapy ($n=26$). Patients treated with intermittent NIV required ETI less often (12 vs. 20, $p=0.03$), had fewer serious complications (13 vs. 21, $p=0.02$), and had a lower ICU mortality rate (10 vs. 18, $p=0.03$) and shorter hospitalization (13 vs. 21, $p=0.02$).

More specifically, in 2012, Anjos et al. [14] studied patients with acquired immunodeficiency syndrome (AIDS) plus AHRF secondary to pneumonia. The authors compared a randomized sequence of NIV using positive end-expiratory pressure (PEEP) (5, 10, or 15 cmH_2O) for 20 min. The results showed a linear improvement in oxygenation with increasing levels of PEEP.

Earlier, in 2002, Confalonieri et al. [15] conducted a prospective case–control study of, more specifically, NIV versus IMV in patients with AHRF secondary to *Pneumocystis jiroveci*. The use of NIV prevented the need for ETI in 67 % of patients and improved survival (100 % vs. 38 %, $p=0.003$). Despite avoiding the use of more invasive devices and having a lower incidence of pneumothorax and shorter stay in the ICU, at 6 months the mortality rate was the same for the two groups.

7.2.2 Influenza Virus A (H1N1) Pandemic

In several countries on all continents, more retrospective [16, 17] than prospective [18] trials have been conducted to study the pandemic caused by influenza virus A (H1N1). The authors discussed their experience with NIV in the approach to AHRF secondary to pneumonia caused by H1N1 virus. Some of the conclusions were contradictory and controversial [18, 19]. We point out two trials that specifically addressed the issue.

In 2010, Liu et al. [20] conducted a retrospective observational study of 18 patients with AHRF secondary to severe pneumonia due to influenza A (H1N1) virus. They found that NIV can improve the patients' respiratory conditions and may lower the mortality (8.3 %) and ETI (24.0 %) rates.

In 2011, Belenguer-Muncharaz et al. [19] conducted a retrospective observational study using NIV in seven (70 %) patients admitted with infection due to

influenza A (H1N1) virus. Overall, 28 % of these patients experienced therapeutic failure with NIV, but there were no fatalities. NIV was effective in 100 % of the five patients in the hypoxemic group, with improved gas exchange and no need for ETI.

7.2.3 Tuberculosis

Thousands of years in existence and catastrophic, tuberculosis has not gotten the same attention as the more recently identified H1N1 infection. Only a few retrospective observational trials [21, 22] have recognized the importance and benefits of NIV in acute respiratory exacerbations in patients with pulmonary tuberculosis sequelae, most of which are in patients with AHRF. Again, non-RCTs have specifically dealt with AHRF secondary to tuberculosis and/or co-infection from pulmonary sequelae.

For example, in 2010 Aso et al. [22] reviewed 58 patients with an acute exacerbation of pulmonary tuberculosis sequelae. Among them, 77.6 % had chronic respiratory failure made acute by co-infections. These patients had all been initially treated with NIV. The mortality for this group with ARF due to co-infections was barely 13.3 %.

7.3 Discussion

Noninvasive ventilation has radically changed the treatment of AHRF, although its use in patients with severe CAP remains controversial (especially in the presence of ARDS). The controversy arises because NIV is associated with higher rates of treatment failure in patients with ARDS-related AHRF than in those with severe AHRF due to other factors. These data suggest that the effectiveness of NIV varies depending on the cause of the patient's AHRF. On the other hand, use of NIV with specific objectives and clear criteria, associated with knowledge of the ventilatory failure predictors to avoid delaying initiation of ETI, make this technique one of the best for patient with conditions such as immunosuppression, COPD, or heart failure.

The selection and exclusion criteria or failure when using the technique are therefore of great relevance for therapeutic success or failure. As a guide, in 2007 the Infectious Disease Society of America/American Thoracic Society [23] recommended ICU admission of patients with severe CAP based on their meeting one of the following major criteria: (1) ARF with IMV requirement and/or septic shock requiring vasopressors; or (2) three of the following criteria: respiratory rate ≥ 30 bpm, $PaO_2/FiO_2 \leq 250$, multilobar infiltrates, confusional state, blood urea nitrogen ≥ 20 mg/dL, leukopenia ($<4 \times 10^9$/L), thrombocytopenia ($<100 \times 10^9$/L), hypothermia (<36 °C), hypotension requiring aggressive fluid therapy.

Regarding criteria for predicting NIV failure in the context of severe CAP, in 2010 Carron et al. [24] conducted a prospective observational study with 64 CAP patients. The authors reported the following as the most significant factors that predicted failure after 1 h of exposure to NIV: increases in the sepsis-related

organ failure assessment (SOFA) score (from 9 to 11), oxygenation index ([FiO_2 × mean airway pressure × 100]/PaO_2) (from 5.0 to 8.6), and respiratory rate (from 23 to 28) as well as decreases in pH (from 7.44 to 7.37) and PaO_2/FiO_2 (from 228 to 127).

As demonstrated by the study's analysis, the best evidence that allows the strongest recommendation about the use of NIV in patients with AHRF secondary to infection comes from studying the subgroup of patients with a chronic underlying condition (e.g., immunosuppression, heart failure, COPD). In this same perspective NIV is recommended in mild infectious situations, unlike severe CAP. Here, although the NIV is not an absolute contraindication, do require a more cautious approach with greater emphasis on the risk–benefit equation and on clinical context due the nosological severity and because there are no sufficiently large, specific and homogeneous RCTs to support its use.

Specifically in patients with AHRF due to influenza virus A (H1N1), NIV is recommended only for less severe forms. This especially applies to patients who have ARDS, who should be treated in a specific room with negative pressure because of the risk of spreading contaminated aerosols. Emphasis should be placed on transmission prevention by using double breathing circuits and basic rules of safety and hygiene (especially hand washing and the use of appropriate masks).

Other forms of AHRF and other infectious agents have been addressed but without enough coherence to generate recommendations. In these cases, the only observations, after critical review and proven experience, is common sense, weighing the risk–benefit equation, and involvement of the patient and/or if he or she is responsive. In the end, one must adhere to the Hippocratic maxim: primum non nocere.

Key Major Recommendations

- The use of NIV in AHRF secondary to infection must obey, as in any other situation, clearly indicated criteria (early onset) during the processes of selection, monitoring, and prognosis failure (appropriate withdrawal without delaying the start of ETI). Also, the operator should pursue clear objectives and improve oxygenation and O_2 delivery (DO_2), relieve dyspnea, and avoid ETI and mortality.
- NIV may be beneficial in patients with AHRF secondary to moderately severe pneumonia in selected cases, especially in immunocompromised patients with heart or lung chronic disease (especially COPD) and when bronchial secretions can be easily controlled.
- Using NIV in patients with severe AHRF due to CAP without meeting these preexisting conditions should be more cautious and under strict monitoring and control (preferably in the ICU) because unnecessary delay in applying ETI after NIV failure increases morbidity.

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Noninvasive Ventilation in the Polytraumatized Patient

8

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Keywords
Noninvasive ventilation • Trauma • Pulmonary contusion • Respiratory failure • Acute respiratory distress syndrome

8.1 Introduction

Trauma is the leading cause of death in persons younger than 44 years of age and is the fourth leading cause of death overall [1]. Approximately 140,000 trauma-related deaths occur in the United States annually. Chest trauma is the cause of death in up to one-fourth of patients with multiple-systems trauma.

The most common traumatic injuries to the chest include rib fractures and flail chest, lung contusion, chest wall hematoma, pleural effusion, pneumothorax, and hematothorax [2]. Pulmonary contusion is especially common in patients sustaining multi-trauma, occurring in approximately 17 % of patients with multiple injuries [3].

Burford and Burbank [4] showed that posttraumatic respiratory failure was caused by an increased amount of interstitial and intra-alveolar fluids. They described it as "traumatic wet lung." The authors recommended that aggressive pulmonary toilet, sufficient pain control, and positive airway pressure by mask be maintained to ensure adequate ventilation. Jensen et al. also reported successful

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treatment of thoracic trauma using continuous positive airway pressure (CPAP) by mask [5].

Subsequent to this trend-setting research, trauma management has been guided according to the mechanism of injury, its anatomical involvement, and the staging of the injury. It has mostly focused on fluid management, pulmonary toilet, control of chest wall pain, and surgical stabilization. Ventilator management has received little attention [6], which is reflected in a low-grade recommendation in the British Thoracic Society (BTS) guidelines for using noninvasive ventilation (NIV) in trauma patients [7].

The efficacy of NIV in the management of respiratory failure due to polytrauma is for the most part ambiguous mainly because of the lack of randomized controlled trials (RCTs) in this population. This chapter reviews current evidence demonstrating the role of NIV in polytrauma patients and suggests an approach for its application based on our own experience.

8.2 Epidemiology of Chest Trauma

Over the last few decades, the escalating number of blunt high-velocity trauma has caused a progressively higher incidence of chest injuries. In fact, 70–90 % of chest injuries in industrialized countries are caused by blunt trauma, with 80–90 % of these cases associated with multi-trauma [8]. High-velocity trauma—e.g., traffic accidents, falls from a height—typically includes severe chest trauma [9]. Profound knowledge of trauma mechanisms and typical injury patterns help reduce the number of missed thoracic injuries.

Flail chest occurs when three or more ribs are fractured in two places or in multiple fractures associated with a sternal fracture. The clinical significance of flail chest varies, depending on the size and location of the flail segment and the extent of the underlying pulmonary contusion. Trinkle et al. showed that respiratory insufficiency associated with flail chest was in fact due to the underlying pulmonary contusion rather than paradoxical respiration [10]. Pulmonary contusion along with chest wall injuries is the most common injury identified in patients with blunt thoracic trauma, and it significantly increases the complication and mortality rates.

The mortality rates among patients with isolated chest injuries are low: 0–5 % for young patients and 1–20 % for the elderly [11]. In severely injured patients with accompanying chest injuries and pulmonary contusion, the mortality rate is reported to be 15–60 %, depending on the overall severity of the injury [12]. Despite a common misconception, pulmonary contusions frequently occur in the absence of rib fractures [13].

Pulmonary contusion is caused by rapid deceleration and a fall, shock waves, or a high-velocity missile. Clemedson reported three mechanisms that are important in the etiology of pulmonary contusions [14]. The “spalling effect” is due to bursting that occurs at the gas–liquid interface, whereas the “inertial effect” occurs when low-density alveolar tissue is stripped from hilar structures as they accelerate at different rates. The overexpansion of gas bubbles after a pressure wave passes is

designated the "implosion effect." Such excess distension can tear the pulmonary parenchyma.

Pulmonary contusion typically promotes the development of acute lung injury (ALI), which may lead to acute respiratory distress syndrome (ARDS). This latter is due to elevated intrapulmonary shunting, ventilation–perfusion mismatching, increased lung water, pulmonary hemorrhage, loss of lung compliance, and release of cytoactive modulators [13]. Miller et al. showed that ARDS developed in 5 % of patients with blunt trauma. The strongest predictors of the development of ARDS were an Injury Severity Score (ISS) > 25 and pulmonary contusion [15].

8.3 Pathophysiology

Direct mechanical damage to the pulmonary parenchyma and the coexistence of indirect systemic and pulmonary sequelae of severe trauma increase the likelihood of complications. Several authors have shown that the severity of pulmonary contusion correlates with the development of pulmonary infections, respiratory failure, and mortality [16] despite the fact that some studies failed to demonstrate a correlation between pulmonary contusion and severe ALI and ARDS [17]. Pulmonary contusion is, however, an independent risk factor for ALI/ARDS, and its severity has been shown to indicate the need for ventilatory support [15]. There are two forms of posttraumatic ALI/ARDS that have been described universally in trauma patients: (1) early ALI/ARDS, which develops within 48 h and is attributed to hemorrhagic shock and capillary leak; (2) late-onset alI/ARDS, which is associated with a higher incidence of pneumonia, often in association with multiple organ failure [18].

The lung is a pliable organ capable of significant deformation. It is highly predisposed to the fracture of blood vessels and parenchymal laceration under briskly applied compressive or concussive loads such as those that occur with pulmonary contusion [13]. Mechanical injuries to the lung can occur through tissue tears when low-density alveolar tissue is stripped from the heavier hilar structures because they accelerate at different rates. The lung can also be damaged by chest wall compression, bleeding into distant lung segments, and direct laceration of the lung through displacement of fractured ribs. Posttraumatic ALI/ARDS is a culmination of intraparenchymal hemorrhage, edema formation, direct mechanical damage to the lung parenchyma, and any additional indirect injuries.

The most characteristic feature of early posttraumatic ALI/ARDS is infiltration of the lung by polymorphonuclear leukocytes (PMNs), akin to other causes of ALI/ARDS [19]. This influx of PMNs into the pulmonary parenchyma and subsequently into the alveolar space in patients with ALI/ARDS is an intricate process. It involves PMN retention, margination, endothelial adhesion within the microvasculature, and finally migration into the alveolar space and pulmonary interstitium. When the PMNs are activated, they can release numerous cytotoxic products. Using a model of the pathogenesis of pulmonary contusion in rats, Hoth et al. [20] showed that the systemic levels of certain chemokines—e.g., monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein-2α (MIP-2α), cytokine neutrophil

chemoattractant-1 (CINC-1)—were significantly elevated at 3 h, with all chemokines significantly elevated at 24 h. Pulmonary expression of interleukin-1β (IL-1β), CINC-1, tumor necrosis factor-α (TNFα), MIP-2α, induced endothelial cell adhesion molecule-1 (ICAM-1), and elastase were increased as well. Also, activated systemic neutrophils showed increased CD-11b. This study illustrated that innate inflammation is activated both locally and systemically.

Eventually, the combination of elastases, proteases, and reactive oxygen species damage the alveolocapillary barrier, resulting in its increased permeability and ultimately in the accumulation of protein-rich alveolar and interstitial edema. Moreover, this high-permeability edema destabilizes airspaces by inactivating the surfactant of alveoli and terminal airways, whose production and function are already significantly impaired [21]. The end result is a combination of several clinical phenomena including increased intrapulmonary shunt, increased pulmonary elastance, reduced functional capacity, hypoxemia, and ventilation-perfusion mismatching.

8.4 Evidence for Noninvasive Ventilation in Polytrauma Patients: Literature Review

Noninvasive ventilation encompasses a range of modes to augment alveolar ventilation without an artificial airway. CPAP and noninvasive positive-pressure ventilation (NIPPV) are the most universally used modes. Two distinct pressure types are used for NIPPV: inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP). In contrast, CPAP maintains a constant positive airway pressure throughout the respiratory cycle.

The benefits of NIPPV in patients with exacerbation of chronic obstructive pulmonary disease (COPD) have been confirmed in several systemic reviews and RCTs. The significant advantages achieved with NIPPV in these patients are largely due to avoidance of invasive mechanical ventilation (IMV) and its complications, including those of the upper airway related to endotracheal intubation (ETI), ventilator-associated pneumonia, ventilator-associated lung injury, ventilator dependence, increased need for sedation resulting in prolonged ventilation, worsening of preexisting infections, and morbidity and mortality [22].

NIPPV in COPD patients with hypercapnic acute respiratory failure (ARF) is now considered a first-line intervention (ahead of ETI and IMV). Several studies have shown that NIPPV in patients with hypoxemic ARF is associated with fewer complications and reduced mechanical ventilation and length of stay in the intensive care unit (ICU) [23]. Patients who are at high risk of nosocomial infection (e.g., immunosuppressed patients, those with hematological malignancies or chemotherapy-induced neutropenia, organ transplantation recipients) are particularly likely to benefit from the use of this noninvasive ventilation mode. Consequently, the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) have issued high-grade evidence-based recommendations in their most recent guidelines for the management and prevention of nosocomial infections, advocating the use of NIPPV whenever

appropriate in the management of ARF and the avoidance of ETI and IMV whenever possible [24].

Ventilatory management in patients with posttraumatic hypoxemic respiratory failure, however, has received little attention because RCTs in this specific population are scarce. The BTS has therefore issued a low-grade recommendation in its guidelines based on the available level C evidence for the use of NIV in polytraumatized patients [7]. The following material reviews some of the critical studies in this specific patient population.

Trinkle was the first to raise the possibility that obligatory mechanical ventilation for flail chest was not necessary [10]. In a small retrospective review with well-matched cohorts, the obligatory ventilation group had a longer hospital stay, a higher mortality rate, and a higher complication rate than a pulmonary contusion (PC) group treated conservatively. This PC group averaged only 0.6 ventilator days, indicating that conservative management was often successful.

The most significant animal study, by Schweiger et al., compared IMV to CPAP in three groups of pigs: a control group, a flail chest (FC) injury group, and a PC/FC injury group [25]. The study showed that the use of 10–15 cm of CPAP was more beneficial than IMV alone for correcting alveolar closure, thereby minimizing the shunt fraction and improving compliance significantly. Furthermore, the need for IMV was significantly reduced after the application of CPAP in all animals, with the effect being more pronounced in the PC/FC injury group than in the isolated FC injury group.

In 2001, Antonelli et al. [26] performed a multicenter survey and showed that patients with posttraumatic hypoxemic respiratory failure responded favorably to NIV, with only a moderate failure rate (18 %).

A multicenter randomized trial by Ferrer et al. [27] was carried out in a mixed population of patients (16 % with polytrauma) with acute hypoxemic respiratory failure. The results only partly elucidated the potential role of NIV in avoiding intubation in hypoxic trauma patients because the cause of the respiratory failure was not randomized.

Tanaka et al. [28] prospectively studied the use of CPAP in 59 patients with an FC injury. The study patients were compared to historical controls treated primarily with mechanical ventilation for respiratory failure. The groups were well matched in terms of extent of chest wall injury and overall injury severity. The CPAP group had a lower rate of pulmonary complications (atelectasis 47 % vs. 95 %; pneumonia 27 % vs. 70 %; $p<0.01$) and a significantly lower rate of IMV use.

Two major RCTs depicted the use of CPAP in patients with severe chest trauma who were not undergoing ETI at the time of presentation. One RCT focused on prevention and the other on treatment of the patients' respiratory failure.

Bolliger et al. [29] conducted the prevention trial in patients with multiple rib fractures who were randomly allocated to one of two groups: (1) a CPAP group (36 patients) given lumbar epidural buprenorphine or an intercostal nerve block with bupivacaine or (2) a group of 33 patients who were treated with ETI and ventilation as well as systemic morphine analgesia. Patients included in both arms of the study had certain conditions in common: hospital admission within 24 h of the injury;

more than three rib fractures; insufficient cough mechanism due to pain or preexisting lung disease. The use of CPAP was compared to intubation/mechanical ventilation. Although the group receiving noninvasive ventilation had a shorter length of stay in the ICU and in the hospital, the design of the study was flawed. It did not reflect current clinical practice: ETI is not in routine prophylactic use in patients similar to those in this control group. Also, one of the exclusion criteria was severe lung contusion. As no computed tomography (CT) images of the chest had been obtained, it is likely that patients with multiple rib fractures had underlying pulmonary contusion not detected by plain chest radiography. On the whole, the two groups were similar at the 5 % significance level except for the ISS, which was higher in the intubated group. The authors believed that this was due to the greater number of blunt abdominal injuries in the intubated group and that the abdominal injuries were considered less severe than the chest injuries in both groups. They thought that the difference was not clinically significant.

In the treatment study, Gunduz et al. [30] executed a randomized study of mask CPAP versus intermittent positive-pressure ventilation (IPPV) via ETI in 52 patients. The results showed that CPAP led to a lower mortality rate (20 % vs. 33 %, $p<0.01$) and a lower nosocomial infection rate (18 % vs. 48 %, $p=0.001$). However, there was no difference in the length of the ICU stay. Also, the small number of patients enrolled and the single-center design raised concerns regarding generalizability.

Hernandez et al. [31] investigated chest trauma-related hypoxemia. The patients were randomized to remain on high-flow oxygen using a mask (25 patients) or to receive NIV (25 patients) using bilevel positive airway pressure (BiPAP) (Respironics, Murrysville, PA). They included patients on oxygen delivered by high-flow mask within the first 48 h after thoracic trauma and with an PaO_2/FiO_2 ratio ≤ 200 for ≥ 8 h. The primary endpoint was intubation. Secondary endpoints were length of hospital stay and survival. The protocol for BiPAP application was well outlined, and the intubation criteria were similarly acceptably defined. The study findings showed that the Acute Physiology and Chronic Health Evaluation II (APACHE II) score was higher in the NIV group ($p=0.02$). However, the study was discontinued early because of the significant difference in the intubation rate: There were less-frequent intubations ($p=0.02$) and later intubations ($p<0.01$) in the NIV group.

In summary, it is evident that there is a lack of Level 1 evidence supporting the ventilatory management of polytraumatized patients with NIV. However, RCTs are starting to appear, although with significant differences in outcomes.

8.5 Noninvasive Ventilation as a Ventilatory Strategy

It is almost impossible to establish universal recommendations for the ventilatory management of polytraumatized patients because of the diversity of this population. The patients are especially at high risk of developing ALI/ARDS [32]. Although the management of decreased alveolar ventilation is usually straightforward and is less challenging than that of posttraumatic ALI/ARDS, delayed or inappropriate management can still precipitate complications.

Atelectasis is one of the most important factors contributing to the development of posttraumatic pulmonary complications. When compensatory mechanisms such as hypoxic pulmonary vasoconstriction become insufficient, atelectasis causes ventilation-perfusion mismatch and hypoxemia refractory to supplemental oxygen. The pulmonary and extra-pulmonary damage can potentially lead to increased morbidity and mortality [33]. Atelectasis also interferes with the clearance of bacteria, such as *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Klebsiella pneumoniae*, which are frequent pathogens in early posttraumatic pneumonia [34, 35]. This deleterious interaction together with the cyclic recruitment and de-recruitment of lung units in atelectatic regions may help explain why injured patients who frequently present with substantial atelectasis are so prone to developing early nosocomial pneumonia [36, 37].

Noninvasive ventilation is definitely beneficial in selected patients, the issue being the choice of patients who will benefit from its use. Identifying patients who should be managed with NIV is challenging, partly because there are few reliable selection criteria. According to the BTS guidelines [7] and the findings of various studies discussed previously, a prudent approach is suggested. It seems sensible to exclude patients who have multiorgan dysfunction or are poor candidates for NIV by virtue of an inability to cooperate or protect the airway or because of excessive secretions. Clearly, NIV should be avoided in patients with shock, severe hypoxemia, or acidosis. A further dilemma is to agree on a threshold of severity for hypoxemia and acidosis beyond which NIV is contraindicated. There are no clear recommendations on this issue, and the application of NIV in such patients with posttraumatic ALI/ARDS should be limited to those who are mostly hemodynamically stable or, alternatively, who can be closely monitored in the ICU, where ETI would be promptly available.

As patients with posttraumatic ALI/ARDS have diffuse alveolar damage and represent those with the most severe form of hypoxemic respiratory failure, the application of optimal levels of NIV can improve oxygenation, relieve dyspnea, and dramatically reduce inspiratory muscle effort [38]. However, one has to balance the NIV that can improve oxygenation on the one hand and increase the pressure support above the CPAP to augment the tidal volume on the other. These effects, however, translate into clinical endpoints of lower intubation rates.

A reasonable clinical approach would therefore be to use NIV judiciously in polytraumatized patients. Although the optimal duration of the initial NIV trial remains uncertain, a reasonable expectation would be a response within 1–4 h of therapy initiation. Finally, patients who are failing an NIV trial should be promptly intubated and mechanically ventilated because delays in starting ETI in patients managed with NIV have been associated with decreased survival [39].

Early conversion to IMV is supported by the finding that the longer atelectasis is tolerated the higher must be the transpulmonary pressures required for reinflation. Also, oxygenation goals accepted for some patient populations may not be acceptable for polytraumatized patients. In contrast to the results of ARDS Network data, hypoxemia on admission is an independent predictor of poor outcome in these patients. For instance, tolerating borderline arterial oxygen tension values such as

55 mmHg can pose a serious threat to patients with a cerebral injury and intracranial hypertension or those at risk of significant bleeding [40].

Many of these patients deteriorate rapidly on the second or third day after the trauma. Thus, intubation and mechanical ventilation become necessary to ensure adequate oxygenation. Such protracted respiratory decompensation corresponds to descriptions of the later-onset alI/ARDS in trauma victims, which demonstrates how the coexistence of several predisposing factors can culminate in respiratory failure [18, 41]. Several authors therefore recommend early aggressive mechanical ventilatory support to prevent diminishing arterial oxygenation and the development of progressive atelectasis [11]. Controlled or assisted ventilatory modes can be chosen if patients must be intubated and ventilated invasively. Putensen and colleagues offered an interesting concept that focuses on maintaining spontaneous breathing. Their reasoning for this approach was that diaphragmatic contractions recruit dependent atelectatic lung regions, which improves both ventilation-perfusion matching and the distribution of ventilation [42].

8.6 Suggested Approach and Recommendations

Figure 8.1 illustrates our approach to integrating the use of NIV into management of the polytrauma patient. Their reasoning is based on the above-mentioned evidence.

In addition to calculating the PaO_2/FiO_2 ratio on supplemental O_2, we have incorporated two other parameters into this algorithm: the ISS and the pulmonary contusion index. The ISS is indicative of the probability that pulmonary contusion increases with the overall severity of the injury. The knowledge obtained can serve as a means to improve the accuracy of diagnosing thoracic injuries and to predict complications [43]. This scoring system may be particularly helpful when sophisticated imaging equipment is not available because early, adequate assessment of thoracic and overall injury severity contributes to being able to initiate appropriate goal-directed management [44].

The third parameter, the pulmonary contusion index, is calculated as the percentage of total lung involvement, as visualized on thoracic CT scans. In addition to providing a qualitative description, this index allows CT risk stratification. Its calculation allows us to assess the degree of lung injury by quantitative analyses of thoracic CT scans [16]. According to Miller et al., patients in whom the volume of the pulmonary contusion measured by CT analysis exceeded 20 % of the total lung volume were at a significantly higher risk of developing ALI/ARDS (82 % vs. 22 %) and pneumonia (52 % vs. 21 %). They also had a significantly higher mortality rate (24 % vs. 3 %) [16].

This approach is therefore beneficial in determining the appropriate positive-pressure therapy used: NIV for moderate respiratory dysfunction and ETI with ventilation and recruitment in patients with severe dysfunction or failed NIV. In patients with severe dysfunction, nonconventional therapies—independent lung ventilation, extracorporeal membrane oxygenation—are alternative choices. Based on the

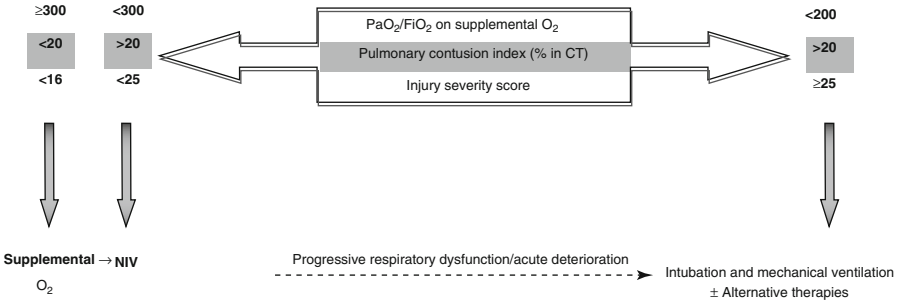

Fig. 8.1 Algorithm of our approach for selecting the appropriate level of respiratory support. These criteria are checked continuously, and the level of support is escalated when necessary, such as in patients with progressively worse respiratory dysfunction. These factors must be considered in conjunction with one another, as the decision between NIV and endotracheal intubation is often complicated. *PaO_2* partial pressure of oxygen in arterial blood, *FiO_2* inspired fraction of oxygen, *CT* computed tomography, *NIV* noninvasive ventilation

current evidence, the transition between the different points of therapy must be determined from further research.

Key Major Recommendations

- Ventilation in polytraumatized patients is challenging because it is difficult to achieve a balance between sufficient ventilation and avoidance of further harm to the lungs.
- Guidelines for the use of NIV in patients with chest trauma recommend CPAP in patients who remain hypoxic despite regional anesthesia. Based on the evidence, however, this recommendation is currently rated as low grade, mostly because of the lack of RCTs in this specific patient population.
- Clinical trials are starting to appear, potentially signaling a reduction in mortality and pulmonary infections based on the fewer intubations required.
- Research is needed to determine the role of NIV in respiratory dysfunction stratification with the appropriate inclusion and exclusion criteria. The application of NIV in trauma patients represents one of the ultimate frontiers in investigating the role of ventilatory support to improve their outcomes.
- The challenging issue is identification of patients who are likely to benefit from NIV, simultaneously avoiding the potential complications associated with delayed ETI.
- Although lower ETI rates and death are typical primary endpoints in randomized trials, in clinical practice the relief of dyspnea, palliation, and comfort are acceptable goals of NIV, especially in patients with a poor prognosis or who refuse advanced life support.

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Noninvasive Mechanical Ventilation in Patients with Severe Pneumonia

9

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Keywords
Noninvasive mechanical ventilation • Pneumonia

9.1 Epidemiology and Etiology

Community-acquired pneumonia (CAP)—pneumonia occurring within 48 h after hospital admission or more than 2 weeks after discharge—leads to hospitalization rates of 20–35 % in Europe, with figures in Spain being even higher at 22–61 %. A substantial proportion of these cases (10 %) are defined as severe. These patients must be admitted to the intensive care unit (ICU) because of the possible need for ventilatory or hemodynamic support. Their mortality rate can be as high as 40 % [1]. In the rest of Europe the incidence of CAP is 5–11 cases per 1,000 person-years, and in Spain it drops to 1.6–1.8 cases per 1,000 person-years, with men and the elderly most often affected and mostly in winter [1].

The etiology of CAP varies according to the geographic area and the population studied. The causal microorganisms also differ depending on whether the patients are admitted to hospital and whether t they require admission to the ICU. An etiological diagnosis is made in 40–60 % of cases. For those admitted to ICU, most

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Spanish and European studies have found that the most common pathogen is *Streptococcus pneumoniae*, followed (although with variability in the percentages and depending on the series of cases) by *Legionella pneumophila*, *Staphylococcus aureus*, and Gram-negative bacilli (GNB). Prevalence is generally lower for *Haemophilus influenzae*, whereas it is the flu virus that most commonly causes CAP. A history of alcoholism or bronchoaspiration suggests an anaerobic or GNB etiology. In patients with chronic obstructive pulmonary disease (COPD), the most common culprits are *H. influenzae*, *Pseudomonas aeruginosa*, and *Moraxella catharralis*. *Aspergillu*s spp. is the least common. In people infected with the human immunodeficiency virus (HIV), *Pneumocystis jirovecii* predominates [1].

Community-acquired pneumonia is generally characterized by signs and symptoms of lower respiratory tract infection accompanied by new infiltrates on chest radiography. In the elderly the symptoms may be limited to confusional states, worsening of underlying illness, or metabolic disorders, which leads to delayed diagnosis in up to 30 % of these patients.

9.2 Pathophysiology

Pneumonia is defined as inflammation of the lung parenchyma caused by various microorganisms leading to accumulation of exudates in the adjacent bronchioles and alveoli. The result is decreased distensibility of the lungs and reduced pulmonary gas exchange.

The main aim of noninvasive ventilation (NIV) in these patients is to improve oxygenation and reduce the workload of the respiratory muscles, thereby alleviating dyspnea. In acute situations such as the pneumonic process, the most important factor determining improvement in the gasometric parameters is the mean airway pressure. Any positive change in the mean airway pressure reflects increased lung volume and consequently a better ventilation/perfusion ratio.

During acute respiratory failure (ARF), there is an extremely close relation between the patient's breathing pattern and the workload imposed on the respiratory muscles. Thus, the more the elastic and resistive loads increase, the greater is the muscle pressure necessary to maintain the same volume and flow. This is illustrated by the equation of motion for gas flow:

$$\text{Muscle pressure} = (\text{elasticity} \times \text{volume}) + (\text{resistance} \times \text{flow})$$

Respiratory failure leads to an increase in the respiratory workload, which is followed by a reduction in circulating volumes and an increase in the respiratory rate.

Positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) essentially increase functional residual capacity, decrease intrapulmonary shunt, recruit alveoli, and improve lung compliance. This chain of events leads to a reduction in the elastic retraction forces that the respiratory muscles have to overcome, thereby reducing the respiratory workload. Pressure support ventilation (PSV) reduces inspiratory effort, and therefore also dyspnea, much more

effectively. Also, because an inverse relation has been observed between the pressure applied with PSV and the respiratory rate, and another directly proportional relation between PSV and the circulating volume, it may also have a beneficial effect on oxygenation. This occurs because it decreases the respiratory workload and oxygen consumption, establishing a better ventilation/perfusion ratio as the result of producing larger tidal volumes. The combination of PSV and PEEP—because it represents an inspiratory aid and counteracts the potential intrinsic PEEP (responsible for the extra effort the inspiratory muscles have to make to overcome the pressure gradient and achieve inspiratory flow)—contributes to reducing the pressure and, consequently, the workload of the respiratory muscles. In clinical practice, it is accepted that the application of both PSV and PEEP can be the most appropriate ventilation method in this situation. So long as a balance is found between the optimal level of PEEP (to improve oxygenation) and the optimal level of PSV (to reduce the activity of the accessory muscles and respiratory rate and improve thoracoabdominal synchrony) the efficacy, at least initially, is similar to that of conventional mechanical ventilation.

9.3 Prognosis

A series of severity criteria from the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) are used in clinical practice to determine the need for ICU admission. A simple points scale, SMART-COP, is now available that seems to predict the need for ventilatory or vasoconstrictor support quite accurately. Also recently published is the REA-ICU scale, which identifies patients who are likely candidates for ICU admission during their first 3 days in hospital (Table 9.1) [1]. The incorporation of inflammatory biomarkers such as C-reactive protein and procalcitonin may improve the predictive capacity of these scales and allow better categorization of patients at high risk of dying [2]. Once in the ICU, the PIRO system, published only a few years ago, correctly identifies those whose lives are seriously at risk [3].

The prognosis depends on a number of factors, such as underlying disease; high Acute Physiology, Age, and Chronic Health Evaluation II (APACHE II) or the Simplified Acute Physiology Score II (SAPS II); hemodynamic status; multiple-organ involvement; nutritional and immune system status; degree of hypoxemia; time since onset; type of germ; both early and correct administration of the antibiotic.

The objective of NIV—defined as the administration of ventilatory assistance without endotracheal intubation—is to provide and ensure adequate ventilation and oxygenation while the medical treatment takes effect. The indications for NIV have been gradually increasing, and it is now used systematically during ARF in patients with COPD, cardiogenic pulmonary edema, or immunosuppression. However, there is a lack of consensus on its use in ARF secondary to pneumonia acquired outside the hospital. In this chapter, we review the available evidence on the application of NIV in patients with CAP.

Table 9.1 Criteria for severe community-acquired pneumonia

ATS and IDSA criteria	SMART-COP scale	REA-ICU scale
Major criteria:		
ARF requiring mechanical ventilation	SBP <90 mmHg (2 points)	Male (1 point)
Septic shock	Multilobar infiltrates (1 point) RR ≥ 25 resp/min for patients ≤ 50 years and ≥30 resp/min for patients >50 years (1 point)	Co-morbidity ≥1 (1 point) RR ≥ 30 resp/min (1 point) Leukocytes < 3×10^9 or ≥ 20×10^9/L (1 point)
Minor criteria:		
Systolic blood pressure (SBP) < 90 mmHg Multilobar infiltrates $PaO_2/FiO_2 < 250$ Confusion BUN (blood urea nitrogen) >20 mg/dL RR > 30 resp/min Leukopenia < 4×10^9/L Thrombocytopenia < 100×10^9 platelets/L Hypothermia < 36 °C	HR > 125 bpm (1 point) Confusion (1 point) Hypoxemia: $PaO_2 < 70$ mmHg or oxygen saturation ≤93 % for patients ≤50 years and <60 mmHg or oxygen saturation ≤ 90 % for patients > 50 years or $PaO_2/FiO_2 < 250$ (2 points) Albumin < 3.5 g/dL (1 point) Arterial pH < 7.35 (2 points)	HR ≥ 125 bpm (1 point) Age < 80 (1 point) Multilobar infiltrates or pleural effusion (2 points) $SatO_2 < 90$ % or $PaO_2 < 60$ mmHg (2 points) Arterial pH < 7.35 (2 points) BUN ≥ 11 mmol/L (2 points) Sodium < 130 mEq/L (3 points)
		Risk of admission to ICU:
The presence of one major criterion or three minor criteria suggest admission to ICU	Three or more points predict the need for ICU	≤3 points 1.1 % 4–6 points 5.5 % 7–8 points 11 % ≥9 points 27.1 %

9.4 Patient Selection: Factors Predicting Success or Failure of Noninvasive Mechanical Ventilation

Although the success of NIV depends primarily on the type of patient selected, there are a number of factors that are predictive of success or failure. Guidelines on NIV recommend using this ventilatory system according to clinical and gasometry criteria, excluding patients for whom it might be contraindicated. Classic potential candidates for NIV are those with a $PaO_2/FiO_2 < 200$ who develop progressive respiratory acidosis with pH ≤ 7.35 and have a sustained respiratory rate (RR) of more than 24 respirations per minute accompanied by active contraction of the accessory muscles or paradoxical abdominal motion. The exclusion criteria are well known. It must be remembered that to try to guarantee success patients must meet a series of criteria before NIV is applied (Table 9.2).

Apart from the variables predictive of NIV failure in patients with hypercapnic ARF, Antonelli et al. [4, 5] described a series of variables in patients with hypoxemic ARF (AHRF) and those who develop acute respiratory distress syndrome (ARDS) that identify those in whom the risk of failure is high. In AHRF patients

Table 9.2 Factors predictive of noninvasive ventilation success

Experience of the medical and nursing teams
Sufficient human resources
Early institution
Adequate instruction and positioning of the patient (sitting up)
Manual fixing of the mask, preventing leaks
Check tolerance and fit of the system (if possible, use helmet in AHRF), with strict "foot of bed" monitoring, especially during the first 6–8 h
Normal facial geometry. Intact dentition
Absence of bronchorrhea
Good neurological status
Haemodynamically stable
Adequate analgesia and/or sedation if agitated (if possible with remifentanil)
Low APACHE II and SAPS II scores
Abnormalities in acid–base balance mild
Adjust PSV and PEEP (4 cm of H_2O in single-tube systems to prevent reinhalation of CO_2) to reduce the RR to <25 resp/min and the activity of the accessory muscles and to achieve a tidal volume of 8 mL/kg
Initially adjust FiO_2 to achieve $SatO_2 \geq 90$ %
Clinical, gasometric, and acid–base balance improvement after 60–120 min of NIV
Try to maintain the NIV for at least the first 24 h without interruption

they are being >40 years of age, SAPS II ≥ 35, $PaO_2/FiO_2 \leq 146$ after 60 min of NIV, and the presence of CAP. For ARDS patients they are SAPS II > 34 and $PaO_2/FiO_2 \leq 175$ after 60 min of NIV.

Various authors have described a number of variables predictive of success or failure of NIV in groups of patients with CAP. In 2010, Carron et al. [6] reported on a small group of patients with severe CAP, regardless of high SAPS II scores, low PaO_2/FiO_2 ratio and low pH on admission, unsatisfactory gasometric response and acid–base balance, and increased respiratory rate and oxygenation index (OI) after application of NIV for 60 min. The OI (mean airway pressure × FiO_2 × 100/PaO_2) is an oxygenation parameter that serves as the most reliable independent predictor of NIV failure in the latter group of patients. In a larger group of patients with H1N1 pneumonia, Masclans et al. [7] reported that involvement of one quadrant on chest radiography, hemodynamic stability, and a Sequential Organ Failure Assessment (SOFA) score <8 are predictors of NIV success. Carrillo et al. [8] also reported that progression of the infiltrate on chest radiography within the first 24 h of NIV, a SOFA score ≥ 7 and heart rate ≥ 104 bpm, $PaO_2/FiO_2 < 144$, and bicarbonate < 23 mEq/L after 60 min of NIV are predictors of NIV failure in patients with severe CAP.

Nevertheless, questions have to be raised while clinical trials are being conducted in patients with AHRF: (1) What patients should be selected, and what criteria should be met to obtain better results? Earlier application of NIV is probably more efficient. (2) What is the role of corticosteroids during the acute phase, and what effect do they have on patients with CAP who undergo NIV [9]? (3) How long

should we wait, and when is the most appropriate time to resort to endotracheal intubation in the event of no improvement after instituting NIV? Most authors generally advise moving on to endotracheal intubation if the recognized standard criteria are met and if no clinical or gasometric improvement is observed within 60–120 min as delay can result in high morbidity/mortality rates.

9.5 Factors Determining Adequate Synchronization Between Patient and Ventilator

Noninvasive ventilation requires a respirator that applies positive pressure resulting in a transpulmonary pressure gradient, adequate tubing system and sensor systems, and above all an interface that adapts perfectly to the patient and enables adequate synchronization of the patient with the respirator. Although the main cause of mechanical failure of NIV is intolerance of the interface. Despite reports of the transparent helmet system improving comfort and reducing complications deriving from this technique, there are a number of factors inherent to the respirator that can critically affect adequate synchronisation. Among these factors are the following.

- *Inspiratory sensitivity*. Flow-triggered inspiration is preferable to pressure-triggered inspiration. If the trigger is too sensitive, the machine auto-triggers (cycles triggered by the ventilator, not triggered by the effort of the patient). With NIV, the auto-trigger tends to occur because of leaks or a poorly fitting interface. The ventilator interprets the increase in flow which attempt to compensate the leak as ventilation demand from the patient, triggering unwanted assisted cycles.
- *Time between the inspiratory effort and flow administration*. The longer the interval, the greater is the respiratory workload. There have been reports of increased delay in the administration of flow in patients receiving PSV with the helmet system, causing a delay between the start of the inspiratory effort and obtaining pressure in the system. This situation has led to discomfort and poor coordination.
- *Inspiratory ramp or flow rate*. In certain situations, a steep ramp allows delivery of flow in less time, reducing the sensation of "air hunger" and onset of the auto-PEEP, thereby making it more comfortable.
- *Expiratory sensitivity*. The patient sometimes terminates the inspiration before the respirator reaches the inspiratory flow-cycle threshold (in PSV, this often happens when 25 % of the peak flow rate is reached). This synchronization fault is called long-cycle asynchrony. In this case, an increase in the expiratory threshold sensor makes it possible to optimize the synchrony between patient and ventilator. In other instances, it may be due to the tidal volume being too high, which would have to be dealt by decreasing the PSV. Short-cycle asynchrony (when the patient's inspiratory time is longer than that of the respirator) tends to occur when chest wall/lung compliance is low or the patient is being underventilated. It can be resolved by reducing the expiratory threshold sensor or increasing the PSV.

- *PEEP valves*. The most suitable PEEP valves are threshold resistors. The external PEEP level necessary to reduce ineffective efforts due to auto-PEEP should never exceed 80 % of the auto-PEEP level. To lessen the problem of auto-PEEP, the bronchodilator treatment can be increased or the PSV reduced.
- *Humidification system*. The most appropriate humidification system is perhaps the surface humidifier (active humidification with an electric guide). Heat and moisture exchangers should be ruled out as they lead to increased dead space and cause an increased respiratory workload.
- *Leak compensation system*. Leaks can cause trigger failure and lengthen the inspiratory time in the PSV mode, leading to intolerance and failure of the NIV. This problem can be resolved by producing the cycle with a secondary safety feature that is usually time-controlled or changing to a pressure-limited, time-cycled ventilator mode.

In general terms, the success of NIV depends on the patient selected and where NIV is applied (i.e., in an ICU), the experience of the team, the type of ventilator (avoiding ventilators that were not designed for NIV), the humidification system and interface used, and adjustment of the ventilator parameters. Applying NIV in patients with ARF secondary to pneumonia should be done exclusively in ICUs because the ICU nursing staff has more experience, the patient can be closely monitored, and endotracheal intubation can be performed if necessary.

9.6 Experience in Acute Hypoxemic Respiratory Failure

Acute respiratory failure secondary to CAP has traditionally been treated with oxygen therapy delivered using face masks. Because of increased respiratory workload and refractory hypoxemia in some situations, however, it has been necessary to resort to endotracheal intubation and connection to mechanical ventilation. In view of the fact that invasive mechanical ventilation is not a risk-free technique and can cause a variety of complications—ventilator-associated pneumonia, complications related to the sedation/analgesia, damage to the trachea and lungs, organ dysfunction—over the last few years the indications for NIV have been extended based on studies that have produced strong evidence for its use [10]. It is now used systematically in patients with COPD or cardiogenic pulmonary edema, those who have undergone thoracic surgery, and immunosuppressed patients.

Although only a small number of patients (13–30 %) with AHRF (defined as ARF caused by a series of processes other than COPD with $PaO_2/FiO_2 < 200$) are potential candidates for NIV. For years now, nonrandomized studies have shown favorable results. Early, however, with the exception of patients with cardiogenic pulmonary edema, improvements were demonstrated only in oxigenation and not in the need for intubation. Wysocki et al. [11] were the first to conduct a randomized trial in patients with AHRF due to various causes, discounting patients with COPD. They compared PSV and PEEP with oxygen therapy and found that NIV did not significantly reduce the endotracheal intubation or mortality rates in the ICU. Upon analyzing the subgroups with $PaCO_2$ below or above 45 mmHg, they found that

these rates were significantly reduced only in those with $PaCO_2$>45 mmHg. Later, among other studies conducted, the multicenter, randomized, prospective study by Delclaux et al. [12] compared CPAP by mask versus oxygen therapy in patients with ARF and bilateral lung infiltrates (due to various causes). Altogether, 54 and 55 % of the patients in the two groups, respectively, had pneumonia. Patients with COPD or respiratory acidosis were excluded. The authors found that although NIV improved oxygenation it did not reduce the need for endotracheal intubation or the mortality rates. Antonelli et al. [13] conducted a randomized, controlled study comparing NIV (PSV and PEEP) with invasive ventilation in immunocompetent patients with ARF (including a small proportion with pneumonia and excluding patients with COPD). They found that NIV improved oxygenation to the same extent as conventional invasive ventilation and significantly reduced both the need for endotracheal intubation (although this was not the primary endpoint) and the number of cases of pneumonia and sinusitis inherent to this invasive technique. Although they found no significant differences between groups regarding the mortality rate (only a trend toward increased survival in the NIV group), it is worth noting that the overall mortality rate was 28.1 % in the group assigned to NIV and 46.8 % in the invasively ventilated group. The Antonelli et al. study stimulated and gave new impetus to the interest in NIV. Since then, a number of randomized, controlled clinical trials have been conducted in both immunocompetent and immunosuppressed patients with AHRF.

Noninvasive ventilation has been shown to have clear clinical benefits in immunosuppressed patients, reducing the need for endotracheal intubation and its inherent complications. However, because of the heterogeneity of the population studied, results in immunocompetent patients have been conflicting owing to the cover-up effect that some AHRF subgroups have over others with a different etiology. Also, no clear improvement was demonstrated in the parameters studied.

We next describe the principal randomized studies conducted on patients with ARF of different etiologies, including pneumonia, in most of which NIV is compared with standard medical treatment. There are also a few studies that compared NIV with endotracheal intubation. We conclude the chapter by discussing studies, both randomized and observational, that focused almost exclusively on patients with pneumonia.

In 2000, Martin et al. [14] published a randomized clinical trial in which they compared PSV and PEEP with standard medical treatment in heterogeneous groups of ARF patients, with and without COPD. They found that NIV significantly reduced endotracheal intubation rates both overall and in the non-COPD subgroup, although it did not decrease the number of days in the ICU or the mortality rate. The results for the COPD group were not statistically significant. These results are in contrast with those of the Wysocki et al. study [11], although it is true that the intubation rate was three times higher in the standard treatment group. This study was pioneering in that it demonstrated that NIV reduces the need for endotracheal intubation in patients with AHRF, suggesting that the benefits of this NIV method are not limited to patients with hypercapnic ARF. These results were subsequently corroborated by a systematic review carried out in 2004 by Keenan et al. [15], who also

stated that it produced a clear improvement, although their study had limitations due to population difference among the patients included. After observing discrepancies, however, they suggested that certain types of ARF should be carefully selected and controlled in the ICU.

Multicenter, randomized clinical trials were published by Ferrer et al. [16] and Honrubia et al. [17]. Ferrer et al. [16] studied patients with AHRF due to various causes (mainly pneumonia, acute pulmonary edema, chest trauma, and ARDS). They included 19 immunosuppressed patients and rejected those with hypercapnia. They compared NIV with high-concentration oxygen therapy, with a primary endpoint of the need for endotracheal intubation. They found that NIV improved oxygenation. Also, it significantly reduced the respiratory rate, the number of intubations, and the mortality rate compared to the control group. It was particularly effective in the subgroup of patients with pneumonia. This contrasted with a previous prospective, cohort study run by Antonelli et al. in 2001 in which pneumonia was identified as one of the predictive factors for NIV failure. This trial was the first to show that NIV reduced the risk of endotracheal intubation in patients with AHRF without chronic respiratory disease.

Honrubia et al. [17] included patients with ARF of various etiologies (pneumonia, cardiogenic pulmonary edema, patients with and without COPD), comparing NIV (PSV and PEEP) with endotracheal intubation. This and the Antonelli et al. study published in 1998 are two of the few randomized trials conducted in heterogeneous groups of patients with ARF in which NIV was compared with endotracheal intubation. The patients in the Honrubia et al. study were older, more seriously ill, and had a lower PaO_2/FiO_2 on admission. The results show a significant (58 %) decrease in the primary endpoint (endotracheal intubation) for those assigned to NIV compared to the control group (100 % of patients intubated). There was also a nonsignificant trend toward lower mortality rates when comparing the two groups and when comparing the group in which NIV failed with those assigned from the start to conventional ventilation. However, subgroup analysis showed that NIV significantly reduced the need for endotracheal intubation in patients with COPD. There was a nonsignificant trend in those who did not have COPD. At the same time, the mortality rates for patients without COPD (57 %) and for those with pneumonia in the NIV group who had to be intubated (50 %)—100 % of those with pneumonia had to be intubated—in relation to those patients assigned to intubation from the time of admission (40 and 80 %, respectively) are all lower than the 90 % rate in those assigned to NIV who required intubation in the Antonelli et al. trial.

Finally, we address the few randomized, observational studies conducted almost exclusively on patients with pneumonia. In 1999, Confalonieri et al. [18] carried out a multicenter, randomized, controlled study with conventional oxygen therapy in patients with ARF secondary to CAP. They found that NIV with PSV and PEEP significantly reduced both the primary endpoint (the number of endotracheal intubations) and the number of days in the ICU. A later analysis revealed that the only ones who benefited were the patients with COPD. These results concur with those of Wysocki et al. [11], who subsequently found, a posteriori, that the greater benefit was in the patients with hypercapnia. Moreover, the intubation rate of 37.5 % in

those without COPD who underwent NIV was slightly lower and nonsignificant in relation to the standard treatment group. This is similar to the findings published by Antonelli et al. in 1998 but with the peculiarity that in the Confalonieri et al. study the APACHE II scale was higher in the NIV group than in the standard treatment group and tended toward statistical significance.

In 2010, Cosentini et al. [19] published a randomized trial conducted in the emergency department in which they compared CPAP using the helmet system with conventional oxygen therapy in immunocompetent patients with CAP. They included patients with $PaO_2/FiO_2 > 210$ but < 285 after wearing a mask with oxygen at 50 % for at least 15 min and excluded those with respiratory acidosis, acute ischemic heart disease, and pulmonary edema. The study had to be terminated prematurely when it was found that the primary endpoint ($PaO_2/FiO_2 > 315$) was achieved in 95 % of patients assigned to CPAP at an average time of 1.5 h whereas in those assigned to conventional treatment only 30 % had reached these levels at 48 h. An important point is that only a few patients managed to sustain the primary endpoint at 60 min and 24 h after CPAP it was discontinued. These results are consistent with those reported by Jolliet et al. [20] and suggest that more sustained application of NIV in accordance with the NIV guidelines, using more comfortable systems such as a helmet, would probably avoid the mechanism of opening and closing of the alveoli and could provide greater benefits.

Among the prospective, observational studies performed, those carried out by Jolliet et al. [20] and Domeniggetti et al. [21] are important. They applied NIV (PSV and PEEP) in patients with ARF. Jolliet et al. [20] included consecutive patients with severe CAP only, excluding those with COPD and cardiogenic pulmonary edema. Domeniggetti et al. [21] included patients with severe CAP and cardiogenic pulmonary edema and excluded those with respiratory acidosis and COPD. Jolliet et al. showed that despite the initial improvement in gasometric parameters, a high percentage (66 %) of patients had to be intubated, with the mortality rate in this group reaching 50 % (none of the nonintubated group died). This was probably due to lower PaO_2 values, the large number of lung lobes affected, and inclusion of older patients compared to other series.

Domeniggetti et al. found that the NIV improved oxygenation and significantly reduced the number of intubations in patients with pulmonary edema (probably because there was more hypercapnia and lower SAPS II scores in that group). The intubation rate (38.8 %) in patients with CAP, although high, was considerably lower than that in the Jolliet group but similar to that found by Confalonieri et al. in the group assigned to NIV without COPD. The more unfavorable data in the CAP group may be the result of both the slow establishment of the initial phase and the lengthy recovery, which is typical of such inflammatory processes in the lungs.

Carron et al. [6] published a prospective, observational study on patients with severe CAP who did not have COPD or cardiogenic pulmonary edema and who received PSV and PEEP with a helmet system. The NIV failed in 56 %, and the mortality rate among those who required intubation was 22 %. This rate is significantly higher than that among patients in whom the NIV was successful but still

lower than the mortality rates in patients from other studies who had to be intubated when the NIV failed. Important points are that patients in whom the NIV failed had a higher SAPS II score, a worse gasometric response, and a significantly shorter NIV application time.

Carrillo et al. [8] studied 184 consecutive patients with severe CAP (82 of whom had a history of heart disease or COPD) who underwent NIV with PSV and PEEP. The NIV was successful overall in 63 % of cases. The mortality rate was 40 % among those with AHRF (who did not have COPD or heart disease) who were intubated after NIV failure. These authors found progressive infiltration on chest radiography during the first 24 h after application of NIV, SOFA score ≥ 7, heart rate ≥ 104 bpm, $PaO_2/FiO_2 < 144$ and bicarbonate < 23 mEq/L 60 min after the application of NIV to be predictors of NIV failure. NIV failure led to an increase in the mortality rate, with an NIV duration ≥ 53 h before intubation being the variable significantly associated with a decrease in hospital survival.

Finally, although NIV has been reported to be effective in isolated cases of pneumonia caused by *Legionella* and in pregnant women with pneumonia and ARF, the results obtained in those with H1N1 virus infection have not been as good as expected. As a result, the European Society of Intensive Care Medicine and a number of studies in Spain [22] have advised against its use. However, Liu et al. [23] and Belenguer-Muncharaz et al. [24], among others, published observational studies with satisfactory, promising results in patients with H1N1 infection, albeit only in a few cases. Moreover, Masclans et al. [7] published the first large-scale, multicenter, observational cohort study of patients with H1N1 viral pneumonia, having excluded patients with COPD or acute pulmonary edema. NIV was applied in 25.8 % of all patients ($n = 685$) and in 36 % of those ventilated. The NIV was successful in 40.6 % of patients. The variables predicting success were involvement of only one quadrant, on the chest radiography, hemodynamic stability, and SOFA score <8. Unlike in other studies, the mortality rate was the same for those in whom NIV failed and those who had been intubated from the start. Nonetheless, a number of important limitations in that study must be pointed out, such as the fact that data were not obtained regarding the severity of the ARF, the lack of standardized criteria for admission to the ICU and intubation, and failure to record the NIV technique and the time elapsed from NIV failure to intubation.

The initial concerns about virus propagation and disease transmission—stemming from the facts that, depending on the type of mask, the amount of leakage, and the inspiratory pressure applied, NIV creates droplets >10 μm within a radius of 1 m—have been gradually diminishing. As a result, the World Health Organization now considers it a reasonable option so long as strict measures are put in place for respiratory protection. In contrast, it is known that the risk of contagion is high when endotracheal intubation must be used [25].

The lack of accord among the studies described can be explained by a number of factors. One such factor is the differences in the populations studied. Others are that some of studies were observational, and some included low numbers of patients. There were also limitations in the interpretation of some of the studies, and in certain cases the subgroup analyses were carried out a posteriori.

Key Major Recommendations

- At present, as stated by Ambrosino and Vagheggini [10], there is firm evidence to support the application of NIV in patients with COPD, cardiogenic pulmonary edema, or immunosuppression. The evidence is weak regarding its use in patients with ARF secondary to asthma, ARDS, or pneumonia.
- Despite the fact that there is less evidence to support the application of NIV in patients with CAP, it can be considered in carefully selected patients but always under close monitoring in the ICU.
- The greatest benefits are perhaps obtained when applied early in patients with early-stage infection by well-trained, experienced teams, when the appropiate modes and interfaces are used, the correct empirical antibiotics are prescribed and, probably, when intravenous corticosteroids are administered.
- Adequately designed studies are required that do not include heterogeneous groups of patients with hypoxemic ARF. The patients should be exclusively those with pneumonia to determine the specific situations in which this ventilation method may be effective.

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Noninvasive Positive-Pressure Ventilation in Patients with Acute Hypoxemic Respiratory Failure and HIV/AIDS

10

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Keywords

Noninvasive ventilation • Acute hypoxemic respiratory failure • Hypoxemic respiratory failure • Respiratory failure in HIV/AIDS • NIV • NIPPV

10.1 Introduction

Pulmonary complications, especially acute respiratory failure (ARF), contribute to morbidity and mortality in immunocompromised patients. The etiology, pathophysiology, and reversibility of lung injury and the severity of ARF are key to the therapeutic response and prognosis for these patients.

An essential notion is that evolution of ARF depends on a causal disease and that noninvasive ventilation (NIV) does not correct the primary process. It should be considered a measure that allows us to gain the time needed to reverse the primary process. The longer NIV is needed, the less chance there is of success, suggesting that perhaps that patient is not an appropriate one to subject to NIV.

It is advisable to identify the various scenarios in which immunosuppression may be associated with ARF.

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- Patients with a malignancy or inflammatory diseases, among whom we can identify two groups: (1) those on immunosuppressive therapy, in whom ARF is mainly associated with infections, recurrence of the underlying disease, drug toxicity, or other noninfectious diseases; (2) those without immunosuppressive therapy, among whom ARF is predominantly related to progression of the underlying disease or other noninfectious disease.
- Transplant patients with predominantly infectious pulmonary complications related to drug immunosuppression, drug toxicity, or other noninfectious diseases.
- Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) patients, among whom ARF is related predominantly to lung infections (bacterial pneumonia, *Pneumocystis jirovecii* pneumonia, lung infections caused by opportunistic agents other than *P. jirovecii*) or other noninfectious diseases.

In HIV/AIDS patients, ARF is the leading cause of hospitalization in intensive care units (ICUs), with bacterial pneumonia and *P. jirovecii* pneumonia the most frequently associated entities. Survival in this situation depends on having the means to diagnose and manage ARF and the causal disease and the methods to support vital functions (including respiratory function) while the causative disease is being reversed. Support of respiratory function might include the use of oxygen therapy, noninvasive positive-pressure ventilation (NIV), intubation and mechanical ventilation (MV), and/or extracorporeal oxygenation devices.

Although MV is an effective, reliable method, it is associated with increased short-, medium-, and long-term morbidity and mortality related to ventilation-associated pneumonia and upper airway injury. Reducing the incidence of these complications associated with effectiveness at least equivalent to that of MV are the rational foundations for the development and implementation of NIV in these patients. Throughout this text, NIV refers to positive-pressure mechanical ventilation without airway invasion. NIV basically includes pressure support ventilation (PSV) with positive end-expiratory pressure (PEEP), also referred to as bilevel pressure ventilation, and continuous positive airway pressure (CPAP).

10.2 Underlying Pulmonary Injury in ARF Patients

The retrospective analysis of 4,710 autopsies of patients who died with ARF (which constituted 18 % of autopsies between 1990 and 2008) showed the following: The patients' average age was 52 years, and 58 % were male. Overall, 38 % of the deceased patients had a single associated disease, 32 % had two, 17 % had three, and 11 % had more than three. In all, 62 % of the patients had two or more associated diseases.

Histopathology revealed lung injury compatible with acute respiratory distress syndrome (ARDS) in 75 % of cases (41 % diffuse alveolar damage, 24 % pulmonary edema, 10 % alveolar hemorrhage). Inflammatory involvement described as interstitial pneumonia (edema of alveolar septa; infiltration with mononuclear cells, histiocytes, plasma cells, and polymorphonuclear neutrophils) was evident in 5 % of cases.

The most frequent associated diseases were bacterial pneumonia in 34 % of cases, malignancies in 28 %, sepsis and/or septic shock in 14 %, and HIV/AIDS in 10 %. The pattern described as interstitial pneumonia was seen predominantly in patients with HIV/AIDS [1].

The retrospective analysis of 250 autopsies of HIV/AIDS patients who died with ARF between 1990 and 2000, showed the following: Histopathology showed acute intersticial pneumonia (edema of the alveolar septa; infiltration of mononuclear cells, histiocytes, plasma cells, polymorphonuclear neutrophils) in 40 % of the cases. It also revealed injuries consistent with ARDS (diffuse alveolar damage 36 %, pulmonary edema 13 %, and alveolar hemorrhage 12 %) in 60 % of the deceased patients.

In addition to HIV/AIDS, a single disease associated with ARF was identified in 40 % of patients, two diseases or more in 44 %, and none in 16 %. Bacterial pneumonia was the most frequently associated disease (36 % of patients), and *P. jirovecii* pneumonia was the second most frequently seen (27 %). Pulmonary or disseminated tuberculosis (TB) was found in 15 %, sepsis and/or septic shock in 14 %, and cytomegalovirus (CMV) pneumonia in 13 %. The most frequent malignant disease was Kaposi's sarcoma, seen in 4.5 % of cases. *P. jirovecii* pneumonia was associated primarily with the injury described as acute interstitial pneumonia and sepsis and/or septic shock with diffuse alveolar damage [2].

Lung infection has a significant impact among the causes of ARF in HIV/AIDS patients. The risk of developing each infection is related to the severity of the immunosuppression, regional epidemiology, and prophylaxis against most frequently isolated agents. A clear example related to regional epidemiology is the comparison of the prevalence of pulmonary TB among different populations. The epidemiology of lung infection has changed in recent decades. Prophylaxis against *P. jirovecii* since 1989 and the availability of highly active antiretroviral therapy (HAART) since 1996 are the most obvious reasons. Although *P. jirovecii* pneumonia has been replaced by bacterial pneumonia as the most common lung infection, both continue to be leaders among causes of ARF.

Infection with HIV increases the incidence of bacterial pneumonia tenfold. Recurrent bacterial pneumonia has been included as an indicative disease for AIDS since 1992. Bacterial pneumonia, especially that caused by *Streptococcus pneumoniae*, and pulmonary TB can develop when the number of CD4+ T-cells is still acceptable (e.g., 500 cells), although the incidence increases as immune function declines. For this reason, during the initial stages of disease Bacterial pneumonia and TB are clearly predominant.

As in the general population, *S. pneumoniae* is the most frequently isolated agent in HIV/AIDS patients with community-acquired pneumonia, 20 % of all bacterial pneumonias, and 40 % of those with isolation of a known agent. Infection by opportunistic agents develops when the CD4+ T-lymphocyte number is <200 cells.

Haemophilus influenzae is isolated in 10–15 % of bacterial pneumonias, especially in patients with significantly lowered immune function. In 30 % of them, the evolution is subacute, and in more than half of these patients there are bilateral radiologically identified lung lesions.

Staphylococus aureus is the third single agent to cause bacterial pneumonia. It is advisable to remember that intravenous drug users may develop endocarditis of the tricuspid valve due to *S. aureus*, with pulmonary seeding manifested by multiple cavitary nodules.

Pseudomonas aeruginosa infections have been significantly reduced. The acquisition of this agent was mostly nosocomial, and patients today have less frequent and shorter hospitalizations. Pneumonias due to *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* appear to be relatively uncommon in this population but have not been systematically studied.

Importantly, there is still a significant population of patients with undiagnosed HIV. There is yet another group with a diagnosis of HIV but who are not taking HAART or any other type of prophylaxis. Both the incidence of infections and related agents continue to be as described before effective treatment came available [3].

A prospective assessment of 57 HIV-positive patients hospitalized with lung injury and ARF between 1993 and 1998 showed the following results: Among the 57 patients, 30 had a diagnosis of bacterial pneumonia and 21 of *P. jirovecii* pneumonia. In all, 23 of the 30 with bacterial pneumonia had CAP. The most frequently isolated agent was *S. pneumoniae*. *Mycobacterium tuberculosis* was isolated in four patients. Most of the patients with *P. jirovecii* pneumonia did not have a diagnosis of HIV and had not received specific prophylaxis or HAART. In all, 33 % of the patients were under HAART compared with 80 % of those monitored regularly in the hospital. Pulmonary lesions seen by chest radiography were bilateral interstitial involvement in 35 patients, bilateral consolidation in 14, and unilateral consolidation in 8. The radiological lesions were bilateral in 100 % of those with *P. jirovecii* pneumonia and in 80 % with bacterial pneumonia. CD4 cell counts in patients with *P. jirovecii* pneumonia compared to those with bacterial pneumonia were 29 and 157, respectively. Mortality in this sample was 40 % and was higher for patients with *P. jirovecii* pneumonia. The only data associated with increased mortality was a low PaO_2/FiO_2 at admission.

Comparing these results with those from previous studies shows that 30 % patients with *P. jirovecii* pneumonia in this study developed ARF versus 70 % in earlier studies of episodes. Only 7 % required intensive care in this study compared with 19 % in the earlier studies. The number and severity of bacterial pneumonias were also reduced after the introduction of HAART [4].

A retrospective evaluation of 147 hospitalized patients with HIV/AIDS and ARF between 1996 and 2006 was conducted. The presence of ARF revealed the diagnosis of HIV in 30 % of the patients. The causes of ARF were bacterial pneumonia in 74 patients (50 %). The most frequently isolated agent was *S. pneumoniae*, with 38 % of these patients developing septic shock. *P. jirovecii* caused pneumonia in 52 (30 %) patients and in 60 % of patients with no previous diagnosis of HIV. Other opportunistic infections were seen in19 patients (12 %), more often TB and noninfectious diseases in 33 patients—predominantly heart failure and chronic obstructive pulmonary disease (COPD), perhaps related to the improved survival of these patients today. Related diseases did not change throughout the study period. Two or more causes were identified in 33 patients (22 %), such as an association of bacterial

pneumonia with *P. jirovecii* or other opportunistic or noninfectious diseases or *P. jirovecii* with CMV. The 43 patients who were under HAART more frequently had bacterial pneumonia or noninfectious diseases than opportunistic infections. In all, 49 patients (33 %) underwent NIV, and 30 % of them required MV. In total, 30 % of patients required MV and 26 % vasopressors. The in-hospital mortality rate was around 20 % and did not change over study period. It was not different for each of the four diagnostic categories. Mortality was related to the need for MV or vasopressors, the greater interval between hospital admission and transfer to the ICU, and the number of causes of ARF. There was no identified association between the CD4 cell count or viral load and mortality [5].

10.3 ARF Physiopathology

Patients with HIV/AIDS develop ARF related to multiple etiologies. Lung injury, however, is limited to a few patterns. We must not forget that ARF treatment through MV can, through alveolar overdistension and cyclical opening and closing of airspaces, generate similar lung lesions. The result of these processes is hypoxemia with or without hypercapnia and multiple organ failure in some cases. Among the described mechanisms of hypoxemia, ventilation/perfusion imbalance and intrapulmonary shunt (i.e., perfusion of alveolar units with little or no ventilation) are typical. They are related to ARDS.

The evolution of ARDS is described in three stages. The *exudative stage* is characterized by alterations in alveolar/capillary membrane permeability and passage of fluid rich in proteins, cytokines [e.g., interleukins 1 and 8, tumor necrosis factor α (TNFα)], lipid mediators (e.g., leukotriene B4), and cells (especially activated neutrophils) to the alveolar space. They are involved in the initiation, maintenance, and progression of an uncontrolled alveolar interstitial inflammatory process. The increased permeability of the alveolar-capillary membrane seems to be a consequence of an alteration in the homophilic union between VE-cadherin molecules, a critical protein in maintaining endothelial cells union. The anti-VE-cadherin antibody, inflammatory mediators such as TNFα, thrombin, and vascular endothelial growth factor (VEGF) interrupt these unions and allow pulmonary edema [6]. Moreover, aggregates of plasma proteins, remnants of necrotic cells, and altered surfactant accumulate, forming intra-alveolar hyaline membranes, which contribute to reducing lung compliance and generating areas of atelectasis. Impaired gas exchange results, causing increased work to breathe and dyspnea.

Pathophysiological phenomena in the pulmonary vasculature can lead to pulmonary arterial hypertension. These phenomena include the following [7].

- Endothelial dysfunction, which involves an imbalance between the vasodilator and vasoconstrictor mediators.
- Pulmonary vascular occlusion, intravascular neutrophil kidnapping, and propensity for intravascular coagulation.
- Increased vascular tone related to alterations in the control of hypoxic vasoconstriction, which generates irregular areas of vasoconstriction and increased

pulmonary vascular resistance, together with vasodilation that exaggerates the ventilation/perfusion imbalance and intrapulmonary shunt. Dysfunctional hypoxic vasoconstriction, which may be correlated with specific factors in the pathological process (e.g., endotoxins, hypothermia, alkalosis, elevated left atrial pressure) or the treatment instituted (e.g., β-adrenergic agonists agents, calcium channel blockers, nitroprusside, PEEP).

- Extrinsic vascular occlusion related to the increase in alveolar volume (PEEP), areas of atelectasis, and alveolar edema.
- Vascular remodeling (in later stages).

During the exudative stage, lung inflammation seems to be driven mainly by activation of the innate immune response through the union of microbial products or endogenous molecules associated with cell damage—danger-associated molecular patterns (DAMPs)—to recognition receptor patterns (e.g., Toll-like receptors) in the pulmonary epithelium and macrophages [8]. Other pathways may also participate, affecting the inflammatory process intensity, such as enzyme converters of angiotensin 1 and 2 balance during the course of viral infections and sepsis [9]. Alveolar surfactant abnormalities, including reduced production, changes in the phospholipid composition, and its inhibition by alveolar plasma proteins promote atelectasis [10].

The *proliferative stage* begins about day 7 and lasts about 2 weeks. During this phase of evolution, most of the surviving patients have been weaned from mechanical ventilation, and lung repair begins. However, in some cases there is progressive lung damage and early changes of pulmonary fibrosis. Histologically, the phase is characterized by organization of alveolar exudates, progressive replacement of neutrophils by lymphocytes, and proliferation of type II pneumocytes over the basal membrane.

Resolution of inflammation requires clearance of neutrophils from the alveoli, a process led by alveolar macrophages and known as "Eferocitosis" [6]. The emergence of alveolar type III procollagen at this stage, a marker of pulmonary fibrosis, is associated with prolongation of the clinical picture and increased mortality.

In the *fibrotic stage*, the alveolar architecture is profoundly altered. Acinar and ductal fibrosis is apparent. It impairs lung compliance and increases alveolar dead space. Fibrotic proliferation of the intima contributes to vascular occlusion, pulmonary hypertension, and its potential impact on right ventricular function [11].

10.4 Physiological Effects of NIV During ARF

The basic objectives of NIV implementation in these patients are to correct pulmonary gas exchange and reduce the work of breathing.

The physiological effects of NIV implementation were evaluated in ten patients with bilateral pulmonary infiltrates associated with lung infections and an average PaO_2/FiO_2 of 131.

CPAP or PEEP of at least 10 cmH_2O significantly increased the PaO_2/FIO_2.

This result suggest that implementation of PEEP or CPAP has favorable effects on oxygenation but only from certain levels. Also, it would be related to the increase

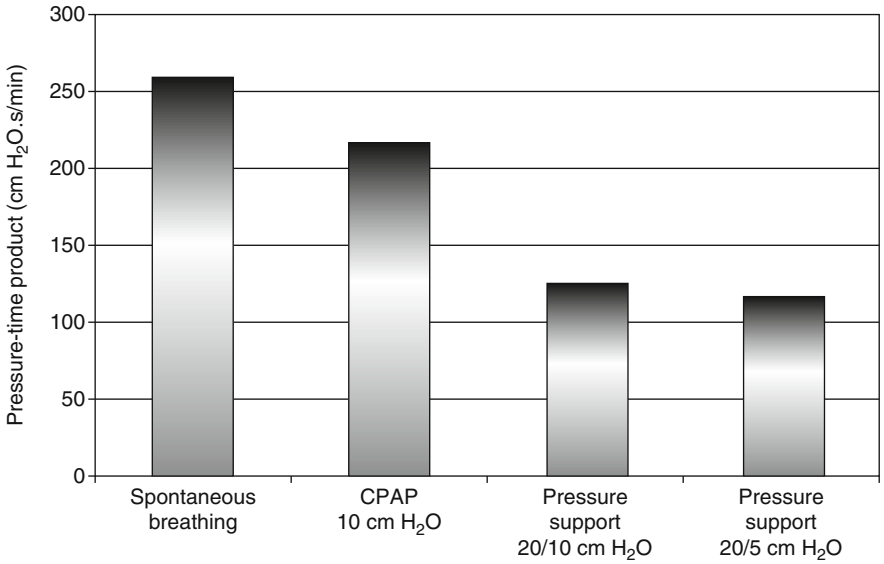

Fig. 10.1 Changes in respiratory muscles loading (pressure–time product) after continuous positive airway pressure (CPAP) application and two levels of pressure support ventilation related to spontaneous breathing in patients with acute respiratory failure [12, 13]

in functional residual capacity, dependent on the alveolar recruitment and stabilization.

Applying a PSV of 10 cmH_2O significantly reduced the PCO_2, alleviated the dyspnea, and reduced the burden on respiratory muscles, work of breathing, and respiratory drive, proportional to the PSV level applied [12].

Through increasing the tidal volume (Vt), NIV and particularly CPAP or PEEP improves respiratory system compliance by recruiting and stabilizing partially or totally collapsed alveoli. The Vt increase is associated with intensity and duration reduction of the respiratory muscles contraction, reducing the work of breathing. NIV reduces the inspiratory effort. The mean esophageal pressure (Pes) was reduced 8–15 cmH_2O (50–76 %), the average transdiaphragmatic pressure (Pdi) by 5–10 cmH_2O (42–62 %), and electromyographic activity of the diaphragm ranging from 17 to 93 %. The diaphragmatic time pressure product (PTPdi) was reduced on average 55 % and the work of breathing by 31–69 %. These results are explained by the reduction in the spontaneous transpulmonary pressure during inspiration (PSV), the threshold load for inspiration that is achieved by balancing the intrinsic PEEP, and the elastic load for inspiration by increasing respiratory compliance (CPAP or PEEP).

The PTPdi and the work of breathing are improved most effectively by combining PSV (10–20 cmH_2O) and CPAP or PEEP (5 cmH_2O), rather than using either alone. In patients with ARF and ARDS, CPAP reduced the PTPdi by about 16 %, whereas the combination of PSV (10–15 cmH_2O) with PEEP (5–10 cmH_2O) reduced it by more than 50 % (Fig. 10.1).

There seems to be no differences in the reduction of the work of breathing if PSV or proportional assisted ventilation applies. Furthermore, the most effective PSV settings for work of breathing reduction (e.g., the pressurization rate, or rise time) are not always the most comfortable for the patient.

Implementation of PSV with values that enable progressive improvement in indicators of the work of breathing reduction is related to a U-shaped tolerance curve. The lowest and highest values have the worst tolerance. The best results are obtained with PEEP values of 0–5 and a PSV of 5 or 10 cmH_2O.

The hemodynamic impact of positive pressure seems to be related to PEEP or CPAP of at least 10 cmH_2O and an interface that does not allow leakage. The operational mechanisms depends on the balance between the reduction of the venous return and afterload for the left ventricle.

The results suggest that the operator should seek the best combination between the levels of PEEP or CPAP and PSV that offer improved oxygenation and relieve stress on the respiratory muscles, limiting the peak pressure (up to 20 cmH_2O) and thus reduce the leaks and facilitate the patient's adaptation to the method [13]. However, the more pulmonary compliance is reduced (as in ARDS), the less are the chances of successful implementation of NIV.

10.5 Patient Selection, Starting, Failure Prediction, Mechanical Ventilation Indications

A reduction in the incidence of nosocomial infection rates is a proven advantage of applying NIV relative to MV in immunocompetent and especially immunocompromised patients. ARF in immunosuppressed patients (who are particularly predisposed to infections, mainly respiratory) is an indication of the need for NIV. According to recent international recommendations, NIV should be used in this context whenever possible [14].

Other noteworthy advantages of NIV are that it does not require the use of muscle relaxants or hypnotics, it allows swallowing and speech, and it does not produce upper airway injuries. Relevant aspects to consider when evaluating the results of starting NIV are team training in NIV indications, considering the importance of correct patient selection; the skills needed for its application (timing and modes); monitoring the trend in the evolution of the disease and the patient's response to the method applied; and finally a comparison of the results obtained by usual care with those obtained in clinical trials with NIV that may show marked differences.

10.5.1 Patient Selection

Patient selection must include consideration of the indications and contraindications for using NIV, both absolute and relative [15]. It is advised that the operator understand the benefits of the method before making decisions regarding the indications and starting it.

Indications for NIV
- Moderate or severe dyspnea
- Respiratory rate of ≥30
- Use of accessory muscles or paradoxical breathing
- $PaO_2/FiO_2 < 200$
- $PaO_2/FiO_2 < 300$ in patients at risk
- Underlying disease reversible in the short term
- Acceptable consciousness
- Hemodynamic stability
- No major organ dysfunction other than the lungs
- Disease categories globally not too high [Simplified Acute Physiology Score II (SAPS II) < 35]

Precautions
- ARDS and pneumonia
- Arrhythmias or cardiac ischemia
- Difficulty managing bronchorrhea

Exclusions
- Respiratory or cardiac arrest
- Lack of patient cooperation
- Uncontrollable vomiting or active gastrointestinal bleeding
- Mask or method intolerance
- Facial deformity or injury that prevents applying the mask
- Immediate orofacial, esophageal, or gastric surgery

10.5.2 Starting Ventilation

For initiating NIV in a patient with ARF [15–17], we recommend the use of equipment that provides a precise, stable FiO_2 and offers the possibility of monitoring the effects of ventilation through graphs and measures. It also should have alarm programming, leakage compensation, and various ventilation modes. The best interfaces are the total face mask, the oronasal mask, or a helmet. The recommended starting mode is PSV with PEEP.

Recommendations for implementation of PSV with PEEP suggest that once the interface is secured the level of PSV should be progressively increased until the expired tidal volume is 7–10 ml/kg and the respiratory rate is <25–35 cycles per minute. PEEP should progressively increase by increments of 2 cmH_2O to reach and maintain the SaO_2 at 90–92 % with up to 10 cmH_2O and an FiO_2 of up to 60 %. The peak pressure should be kept below 20–25 cmH_2O. Ideally, the patient is monitored continuously during the first 24 h. *Strict monitoring of the patient's evolution is needed in all units where NIV is being applied.*

Note: Based on the patient's evolution and tolerance, periods of spontaneous breathing can be initiated, with special care to avoid too rapid progress, which is usually harmful.

10.5.3 Failure Prediction

Several factors can predict NIV failure [15–17].
Age > 40 years
ARDS or NAC
SAPS II ≥ 35 or APACHE II ≥ 17
Respiratory rate > 25 at 1 h after NIV was initiated
Shock
Severe hypoxemia at admission
$PaO_2/FiO_2 \leq 175$ at 1 h after starting NIV

10.5.4 Indications for MV [15–18]

There are several indications for switching from NIV to MV [15–18].
Failure to maintain PaO_2 of 60 mmHg on FiO_2 of 60 %
Requirement of high pressure peaks
Lack of improvement trend regarding dyspnea and/or gas exchange
Mask or method intolerance
Difficulty managing respiratory secretions
Hemodynamic deterioration
Neurological impairment

10.6 Results

Numerous studies have confirmed the effectiveness of NIV in patients with COPD, acute hypercapnic respiratory failure, and cardiogenic pulmonary edema. Studies that have evaluated results in noncardiogenic hypoxemic ARF are scarce, as are those that have analyzed results of NIV implementation for ARF in immunosuppressed patients, HIV/AIDS, or other conditions. It is advisable to note that there is a considerable gap between scientific evidence and actual clinical situations to evaluate results of this method.

Consider a patient with HIV/AIDS in the emergency room with dyspnea and fever of 24 h, tachycardia, tachypnea, hypoxemia, and bilateral lung consolidation. We are subject to numerous limitations on data that would be needed to support decision making in this case, including current deterioration, degree of immunity, etiology of the disease, lung injury in evolution (pneumonia, ARDS, alveolar hemorrhage, or some combination), histopathology (acute interstitial pneumonia, diffuse alveolar damage). The need to make immediate decisions must be considered when overlaid with the data provided by the literature and their impact on the final result, rather than the efficacy of NIV itself. The parameters used by researchers to evaluate the results of NIV application during ARF includes clinical variables, measures of gas exchange, duration of hospitalization, need for MV, complications, and survival. The study designs have been heterogeneous with respect to patient and control selection and globally are grouped into two categories: NIV compared to conventional treatment for ARF (drug and oxygen therapy) or NIV compared to MV.

Starting NIV early during ARF has proved crucial for better results in immunosuppressed patients without HIV/AIDS [19, 20]. In a group of patients with ARF, among whom 20 % were immunosuppressed, Torres et al. showed that NIV is better than oxygen therapy in terms of improving the respiratory rate, oxygenation, need for MV, incidence of septic shock, and short-term mortality [21].

Uncontrolled studies evaluated CPAP and PSV in *P. jirovecii* pneumonia-related ARF and demonstrated a significant improvement in parameters such as dyspnea, respiratory rate, and gas exchange. They were associated with a reduction in MV indication and mortality [22–25].

Hilbert et al. established the effectiveness of NIV during ARF in immunosuppressed patients compared to conventional treatment in terms of MV indication (46 % vs. 77 %), short-term mortality (38 % vs. 69 %), and in-hospital mortality (50 % vs. 81 %). The number of HIV/AIDS patients in this sample was low [17].

Antonelli et al. randomized immunosuppressed patients (solid organ transplantation) with ARF to receive NIV or conventional treatment. They showed that NIV reduced the rate of MV indication (20 % vs. 70 %), ICU stay (5.5 vs. 9.0 days), and ICU mortality (20 % vs. 50 %). There was no difference in hospital mortality [26].

Confalonieri et al. showed that NIV and MV are equally effective in improving the respiratory rate and gas exchange in *P. jirovecii* pneumonia patients. Both methods significantly reduced the rate of associated complications [27].

In noncontrolled studies of ARF and *P. jirovecii* infection in immunosuppressed HIV/AIDS patients, the success rate for avoiding MV was 72 % with CPAP and 77 % with PSV. With NIV patient survival was 100 % versus 38 % for patients who required MV [28].

Dantas Anjos et al. demonstrated that CPAP improved gas exchange (oxygen) PSV, relieving the sensation of dyspnea in patients with HIV/AIDS during ARF [29]. Starting NIV during ARF, both moderate and severe, reduced the number of MV indications by 23 %, the ICU stay by 2 days, and short-term mortality by 17 % [30]. Both studies showed the benefit for NIV compared to MV. The results of studies showing noninferiority of NIV when considering conventional parameters can be regarded as results in favor of applying NIV, especially if we also take into consideration the avoidance of complications associated with MV, mainly respiratory infections [31, 32].

Key Major Recommendations

- Even if NIV seems to be a simple method with encouraging results and of low risk, it is important to note that these features are dependent on the technique being employed by an optimally trained and updated team. Success also depends on properly selected patients, the method being suitably applied, and, especially, failure quickly acknowledged.
- Not recognizing failure of the method to obtain the desired results and delay in applying MV in a timely fashion are main sources of serious complications related to NIV.

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Noninvasive Ventilation for Severe *Legionella* Pneumonia

11

Turgay Çelikel

Keywords
Noninvasive ventilation • *Legionella* • Pneumonia

11.1 Introduction

Legionnaires' disease was first recognized at the 1976 American Legion Convention in Philadelphia, in which 182 American Legionnaires contracted pneumonia and 34 individuals died [1]. Investigators from the Centers for Disease Control and Prevention (CDC) subseqently identified the causative agent as an aerobic Gram-negative bacterium and named it *Legionella pneumophila*. During the last three and a half decades, *L. pneumophila* has become widely recognized as a cause of community-acquired pneumonia (CAP) in patients who required intensive care unit (ICU) admission. In many studies, the clinical manifestations for legionnaires' disease were more severe and the mortality was higher when compared with pneumonias of other etiologies. This may be due to a delay in diagnosis and suboptimal antibiotic therapy rather than enhanced virulence of *L. pneumophila*. Strains of *L. pneumophila* differ in virulence. *L. pneumophila* causes more severe disease than other bacterial pathogens associated with acquired pneumonia. The mortality associated with Legionnaires' disease is notably higher than that the other atypical pneumonias in which *L. pneumophila* is included (*Chlamydia pneumoniae* and *Mycoplasma pneumoniae* are the others). Mortality is similar to that of bacteremic pneumococcal pneumonia.

Legionella bacteria are cleared by the mucociliary process in the upper respiratory tract. This explains the consistent epidemiological association of legionnaires' disease in cigarette smokers, patients with chronic pulmonary diseases, and

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alcoholics in whom mucociliary clearance is impaired. Legionnaires' disease is more common and more severe for patients with depressed cell-mediated immunity, including transplant recipients, patients receiving corticosteroids, and patients with acquired immunodeficiency syndrome (AIDS).

Initial reports of the clinical manifestations of *Legionella* infection presented the picture of a severe, progressive pulmonary infection with prominent extrapulmonary complications. In the 1976 outbreak, renal insufficiency (15 %), altered sensorium (21 %), and gastrointestinal symptoms, particularly diarrhea (41 %), were noted. Overall mortality was 21 % [1]. Because *L. pneumophila* was at that time unknown as a pathogen, the majority of patients received ineffective antibiotic therapy. Subsequent studies directly comparing legionnaires' disease with pneumonia of other etiologies have shown that *Legionella* infection is not readily distinguishable from that caused by other organisms based on clinical presentation [2]. The incubation period is 2–10 days after exposure. The patient may experience a brief prodrome of malaise, fever, chills, and nonproductive cough. Myalgias are a prominent complaint. The symptoms generally progress until the patient presents for medical care. The median time to presentation from onset is 4 days. About 90 % of patients are febrile at presentation. Chest pain is present in one-third of patients, and dsypnea is seen in 60 %. Cough is typically nonproductive at first, although one-half of the patients produce sputum after several days of illness. Respiratory failure requiring ventilatory support occurs in 15–50 % of patients [3].

Laboratory findings are nonspecific. The majority of patients have leukocytosis in excess of 10,000 cells/mm^3 with a left shift. Hyponatremia was a prominent manifestation in several studies. In recent series, elevated creatinine kinase levels have been reported in 30–50 % of patients [2]. Elevated hepatic transaminases and elevated serum creatinine have been described. Comparative studies with pneumonias of other etiologies indicate that no laboratory findings exist that specifically point to a diagnosis of *Legionella* infection [3, 4]. The typical progression of radiologically seen chest infiltrates, despite adequate therapy, can be misleading. There is an association between the extent of radiological involvement and the onset of respiratory failure. However, in patients receiving effective treatment from the onset, radiographic progression of infiltrates is limited to 30 % [5]. The following clinical observations should heighten clinical suspicion of Legionnaires' diseae: (1) fever exceeding 39 °C; (2) presence of diarrhea; (3) Gram's stain of sputum with presence of neutrophils, but few if any organisms; (4) hyponatremia (serum sodium $\leq$ 130 mEq/L); (5) failure of a therapeutic response to β-lactam (penicillin or cephalosporin) or aminoglycoside antimicrobial agent; (6) occurence in a setting of known contamination of potable water with *Legionella* [6].

Numerous studies of CAP over the past three decades have produced consistent results regarding the likely etiological agents in immunocompotent individuals. A review article analyzed 19 prospective studies reporting 6,845 patients with CAP who required hospitalization. *Streptococcus pneumoniae* was the most common bacterial pathogen identified worldwide. *L. pneumophila* was ranked among the top five most common causes of CAP in 12 of the 19 studies [6]. If the patient was admitted to the ICU, the organism was considered to be among the top five most

common causes in eight of nine studies [6]. Legionnaires' disease also can be seen as a nosocomial pneumonia, but it is underdiagnosed because cultures on multiple selective media are generally not available inside hospitals.

The term "severe CAP" identifies a group of patients with severe disease who are prone to have complications and poor outcomes, and who require a higher level of care [7]. Ewig and Torres suggested that a combination of hypotension, multilobar involvement apparent on a chest radiograph, arterial hypoxemia, and mechanical ventilation (MV) need be used to define severe pneumonia [8].

Vergis et al.'s review article focused on nine studies that reported 890 cases of CAP for which admission to the ICU was required. In that review, *S. pneumoniae* and *L. pneumophila* were the most frequently identified etiological agents. In these nine studies, the frequency of MV among patients with severe pneumonia ranged from 9 to 91, the mean mortality rate among MV patients was 35 % (range 31–42 %) [6]. The mortality rate in the nine series ranged from 8 to 29 %, and that for severe Legionnaires' disease was 0–25 % [6]. El-Ebiary et al. analyzed prognostic factors for severe *Legionella* pneumonia requiring ICU admission. There were 33 nosocomial cases and 51 CAP cases of *L. pneumophilia* pneumonia. In all, 64 % of these patients required MV. Mortality was 30 %. There was no difference in mortality rates between nosocomial and CAP cases. The univariate analyses showed that cardiac disease, diabetes mellitus, creatinine $\geq$1.8 mg/dL, septic shock, chest radiologically diagnosed extension, MV, hyponatremia $\leq$136 mEq/L, and blood urea levels $\geq$30 mg/dL were factors related to poor outcome. Adequate treatment for *Legionella* pneumonia and alleviation of the disease were related to a better outcome [9].

Weak evidence supports the use of noninvasive ventilation (NIV) in patients with acute respiratory failure (ARF) due to pneumonia and acute respiratory distress syndrome (ARDS). Meduri et al., in their 1996 case series, reported 11 patients with severe CAP and without chronic obstructive pulmonary disease (COPD). Intubation was necessary in four (36 %) of these patients. Management of secretions was the main reason for intubation. One patient could not tolerate the mask. When patients with COPD and pneumonia were included, a total of 41 patients with pneumonia entered the study. Intubation was required in 15 (36 %). In only three patients was intubation due to inability to clear secretions [10].

A prospective survey conducted in 70 French ICUs highlighted a possible increase in the mortality rate in a subgroup of patients with de novo hypoxemic ARF not related to acute cardio pulmonary oedema (CPO) or acute exacerbation (AE)COPD and treated with NIV, perhaps due to delayed endotracheal intubation (ETI) [11]. Joliet et al. reported failure rates up to 66 % in patients with severe CAP [12] supported with NIV. In their study, NIV acutely improved oxygenation and reduced breathing rate in all patients. Despite this initial transient improvement, however, two-thirds of the patients eventually required intubation and MV with a short mean delay (1.3 days) between admission and intubation. The patients who were subsequently intubated were older (55 $\pm$ 15 vs. 37 $\pm$ 12 years) and more severely hypoxemic (63 $\pm$ 11 vs. 80 $\pm$ 15 mmHg, $p < 0.05$) than those not requiring intubation. Eight patients died (33 %), all of whom were in the intubated group. The causative agent

in 1 of these 24 cases of severe CAP was *L. pneumophila*. This 38-year-old man had involvement of three lobes. His Acute Physiology, Age, and Chronic Health Evaluation (APACHE II) score was 9, PaO_2/FiO_2 68, $PaCO_2$ 38 mmHg, and pH 7.42. After an NIV trial, he was intubated during the first day of ICU admission and survived. The authors concluded that the more favorable outcome and shorter ICU and hospital stays when intubation is avoided, as well as the short delay required to assess the success or failure of NIV, warrants a trial of NIV in this setting.

Confalonieri's randomized controlled trial (RCT) of patients with severe CAP showed that NIV reduced ETI rates, ICU length of stay, and 2-month mortality rate—but only in the subgroup with underlying COPD [13]. A microbial diagnosis of pneumonia was established in 32 (57 %) patients. Cause of pneumonia was *L. pneumophila* in two of these cases.

Ferrer et al.'s RCT of patients with hypoxemic ARF showed that NIV reduced the need for ETI, the incidence of septic shock, and the levels of tachypnea and arterial hypoxemia. It also improved the ICU and 90-day survival rates compared with patients receiving high-concentration oxygen therapy [14]. Interestingly, in this study NIV was especially effective in the subset of patients in whom pneumonia was the cause of respiratory failure. This was the first study showing that NIV can reduce the rate of intubation in patients with pneumonia mainly without chronic respiratory disorders. In contrast, another RCT found that NIV reduced the need for intubation in patients with severe ARF with the possible exception of pneumonia [15].

In a meta-analysis, pneumonia was not identified as a risk factor for noninvasive ventilation [16]. Studies of NIV for the treatment of acute lung injury (ALI)/ARDS have reported failure rates of 50–80 %. Independent risk factors for NIV failure in this group of patients included severe hypoxemia, shock, and metabolic acidosis [17, 18]. A meta-analysis of ALI/ARDS reported an NIV failure rate of almost 50 % in patients with ALI/ARDS. The authors suggested that NIV be cautiously used in patients with ALI/ARDS [19].

A recent multi-center European survey reported the application of NIV as a first-line intervention in patients with early ARDS. They described the everyday clinical practice in three European ICUs that had expertise with NIV (patients with failure of more than two organs, hemodynamic instability, or encephalopathy were excluded). The use of NIV improved gas exchange and avoided ETI in 54 % of the patients. Avoidance of ETI was associated with a lower incidence of ventilator-associated pneumonia (VAP) and a lower ICU mortality rate. The need for ETI was more likely in older patients, those with a high Simplified Acute Physiology Score II (SAPS II) score, those severe hypoxemia, or when a higher level of positive end-expiratory pressure (PEEP) and pressure support were needed [20].

"The Berlin Definition of ARDS" article defined NIV as a therapeutic option for patients with mild ARDS ($PaO_2/FiO_2 > 200$ but < 300). The committee believed that the new PaO_2/FiO_2 threshold chosen for the different levels of ARDS severity could be helpful for categorizing patients with respect to the various therapeutic approaches [21].

Carillo et al. prospectively assessed 184 consecutive patients with severe ARF due to CAP and initially supported with NIV [22]. Among them, 102 patients had de novo ARF, and 82 had previous cardiac or respiratory disease. Patients with de

novo ARF failed NIV more frequently than patients with previous cardiac or respiratory disease (46 % vs. 26 %, $p=0.007$). Worsening radiologically determined infiltration 24 h after admission, a maximum Sepsis-Related Organ Failure Assessment (SOFA) score and after 1 h of NIV, high heart rate, and low PaO_2/FiO_2 and bicarbonate independently predicted NIV failure. Similarly, maximum SOFA, NIV failure, and older age independently predicted hospital mortality. In patients with de novo ARF, long-duration NIV before intubation was associated with low hospital survival. This association was not observed in patients with previous cardiac or respiratory disease. The authors concluded that succesful NIV was strongly associated with better survival. They also noted that to minimize mortality delayed intubation should be avoided in patients with de novo ARF particularly when they require vasoactive drugs, a condition associated with NIV failure in patients with ALI.

Successful treatment with NIV, which is reflected in less organ system failure and a good initial response to antimicrobial treatment, is strongly associated with better survival. If predictors of NIV failure are identified in patients with de novo ARF, it is strongly advised that there be no delay in intubating the patient, thereby minimizing the chances of death.

As already noted, *Legionella* infections frequently result in severe pneumonia and ARDS requiring MV support. We recently managed a severe case of *Legionella* pneumonia using NIV in our medical ICU [23]. Going through this case points out practical clues in the management of severe *Legionella* pneumonia.

A 34-year-old man was admitted to the emergency room for severe pneumonia and ARF. He had a cough with yellow-green sputum production, fever, mild dyspnea, nausea, vomiting, oliguria, and diarrhea for 5 days before admission. Body temperature was 40 °C. The diarrhea was nonbloody with a frequency of 10–15 times per day. On the day before admission, he was seen at another hospital because of worsening dyspnea. Chest radiography revealed dense multi-lobar consolidations. Because severe CAP requires treatment at an ICU, he was referred to our hospital. Upon arrival at the emergency room his vital signs were as follows: respiratory rate 30 breaths/min, pulse 120 beats/min, blood pressure 110/80 mmHg, body temperature 37.2 °C. His oxygen saturation was 83 % on breathing room air. He was conscious. No lymphadenopathy was detected. Inspiratory crackles were heard at both mid and lower lung zones. There was no peripheral edema or digital clubbing. The heart and abdomen were normal. Maculas and papules of 1 mm diameter were present over his arms and legs.

Findings of the neurological examination were unremarkable. Chest radiography revealed the presence of multilobar pneumonia (Fig. 11.1). The patient was transferred to the ICU because of severe CAP (respiratory failure requiring MV, PaO_2/FiO_2 127, respiratory rate >30/min, multilobar pneumonia).

The patient was a taxi driver, and his medical history was not remarkable. He used to drink small amounts of alcohol and had been smoking 44 packs/year. He had no travel history.

Upon arrival in the medical ICU, vital signs were as follows: respiratory rate 40 breaths per minute, pulse 130 beats per minute, temperature 38.2 °C, blood pressure

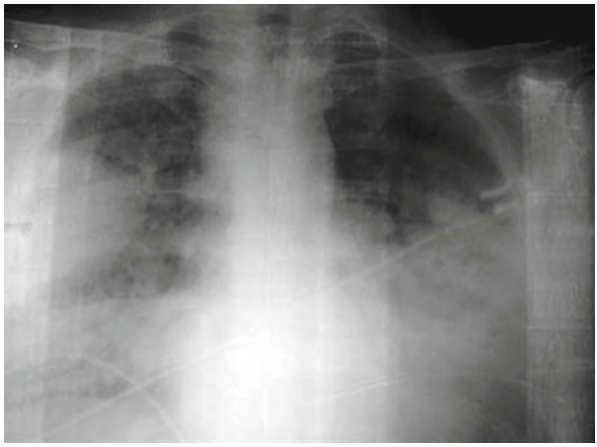

Fig. 11.1 A 34-year-old man with bilateral *Legionella* pneumonia

110/58 mmHg. Laboratory results were remarkable, with a leukocyte count of 11,300/mm^3 and creatinine 7. 4 mg/dL. Oxygen administration was commenced and arterial blood gas analysis revealed the following: pH 7.32, PaO_2 51 mmHg, $PaCO_2$ 31 mmHg, HCO_3 16 mmol/L, PaO_2/FiO_2 127. The APACHE II and Murray lung injury scores were 20 and 7, respectively. The patient was diagnosed with ARDS due to severe CAP. The specific urinary antigen test for *L. pneumophila* was positive.

Clarithromycin 500 bid IV and rifampicin 600 mg PO were started. A drug reaction characterized by macular skin rashes developed. These lesions disappeared with local steroidal and antihistaminic treatment.

In the ICU, the patient developed tachypnea (respiratory rate 52/min) and severe respiratory distress ($PaO_2/FiO_2 < 200$). NIV was commenced: bilevel positive airway pressure (biPAP), full-face mask, inspiratory/expiratory ositive airway pressure (IPAP/ EPAP) 20/8, FiO_2 55 %. Acidosis could not be corrected by BiPAP, and the oxygen need of the patient increased. Treatment with a Puritan Bennett 7200 ventilator was initiated to be able to achieve a higher FiO_2 and for a better control over the tidal volume. NIV support with the Puritan Bennett 7200 attained a 20 % decrease in respiratory rate and symptomatic relief. The need for NIV gradually decreased during the following days (Table 11.1). Renal functions of the patient returned to normal levels with fluid replacement and medical treatment. His temperature continued to be high, and enterococci were detected in one of successive blood cultures. Teicoplanin 1×400 mg IV was added to the treatment, and his temperature decreased. During the follow-up in the ICU, the need for oxygen gradually decreased, and NIV was stopped on ICU day 13. The patient was then transferred to the ward.

As illustrated in this case, patients with severe pneumonias should be admitted to the ICU and monitored closely. Choosing the right antibiotic that covers atypical pathogens and applying it as soon as possible is probably the most important part of correct management. NIV should be started early if there is respiratory distress. If equipment is available, it should be started with a ventilator specifically designed to apply NIV and can monitor exhaled tidal volume and administer FiO_2 up to 1.0.

Table 11.1 Progress chart of a patient with severe *Legionella* pneumonia

		ICU							
	ER	0 h	7 h	8 h	16 h	Day 3	Day 8	Day 11	Day 12
FiO_2	0.21	0.40	0.40	0.40	0.55	0.55	0.30	0.30	0.30
Ventilator	–	–	BiPAP S	BiPAP S	Puritan Bennett 7200	Puritan Bennett 7200	Puritan Bennett 7200	Puritan Bennett 7200	Puritan Bennett 7200
Mode	–	–	BiPAP	BiPAP	CPAP	CPAP	CPAP	CPAP	CPAP
RR	40	40	40	40	49	31	37	26	24
Pressure support	–	–	12	12	20	25	30	15	15
PEEP	–	–	8	8	8	8	6	5	5
PaO_2	51	51	76	90	87	80	66	83	83
$PaCO_2$	26	31	31	35	31	33	38	34	34
HCO_3	14.3	16	15.5	15.5	15	17	24	21	21.6
pH	7.36	7.32	7.30	7.26	7.27	7.32	7.40	7.39	7.40
PaO_2/FiO_2	242	127	190	225	158	145	220	276	276

FiO_2 fraction of inspired oxygen in a gas mixture, *ER* emergency room, *BiPAP* bilevel positive airway pressure, *CPAP* continuous positive airway pressure, *RR* respiratory rate, *PEEP* positive and expiratory pressure, *PaO_2* arterial oxygen pressure, *$PaCO_2$* arterial carbondioxide pressure

Simple BiPAP devices designed for domicilary use, as shown in this case, will most likely be unsuccesful because they cannot deliver high concentrations of oxygen. Most new ICU ventilators have NIV modes. The older ICU ventilators can be used in pressure support or pressure control modes. However, not all ICU ventilators show the same performance during NIV because of mask leaks. If a patient does not tolerate NIV with one ventilator, it is helpful to change to a different kind of ventilator. Another important point is close monitoring of the patient's ICU progress under NIV. The patient should show improved pH, PaO_2, $PaCO_2$ and respiratory rate within a few hours. If this improvement is not seen, the patient should be intubated without delay.

Legionella pneumophila is one of the most common etiological agents in patients with severe CAP requiring admission to the ICU. Up to 64 % of these patients may need MV support. Mortality can be as high as 30 % [9]. The use of NIV in patients with severe pneumonia and ARDS is controversial. Infection Disease Society of America/American Thoracic Society guidelines on the management of CAP state that patients with hypoxemia or respiratory distress should undergo a cautious trial with NIV unless they require immediate intubation because of severe hypoxemia [arterial oxygen pressure/fraction of inspired oxygen (PaO_2/FiO_2) < 150] and bilateral alveolar infiltrates *Note that this is a* "*moderate recommendation*; *level III* (*low*) *evidence*" [24]. NIV for this indication should be applied in the ICU with NIV ventilators capable of giving FiO_2 1.0. Also, the patient must be monitored closely, and frequent arterial blood gas assays should be done. If a patient does not show improvement in a few hours, he or she should be intubated. Delayed intubation has been shown to increase mortality in this setting [25, 26].

Key Major Recommendations

- *Legionella pneumophila* is one of the most common etiological agents in patients with severe CAP requiring admission to the ICU. Mortality can be as high as 30 %. The use of NIV in patients with severe pneumonia and ARDS is controversial. NIV for this indication should be applied in the ICU with ventilators capable of giving FiO_2 1.0. A cautious trial of NIV can be given unless the patient requires immediate intubation. If a patient does not show improvement in a few hours, he or she should be intubated. Delayed intubation has been shown to increase mortality in this setting.

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Noninvasive Mechanical Ventilation in Lung Injury Secondary to Malaria

12

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Keywords
Malaria • ARDS • ALI • Acute respiratory distress syndrome • *Plasmodium* • Falciparum • Vivax

12.1 Introduction

Malaria is an infectious disease caused by one or more of several species of the protozoan parasite *Plasmodium* including *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* [1] and occasionally other *Plasmodium* species, notably monkey malaria *P. knowlesi* [2]. The infection is primarily transmitted by the bite of an infected *Anopheles* mosquito but may also be transmitted via transfusion of infected blood products and congenitally. Malaria is a global public health problem with the highest burden in tropical and subtropical countries including India. In 2010, an estimated 3.3 billion population were at risk for malaria, with 216 million cases diagnosed and 655,000 deaths. Most deaths occurred in African children [3]. India accounts for 66 % of the 2.4 million confirmed malaria cases in Southeast Asia, with *P. falciparum* causing 50 % of them. Malaria is imported into temperate zones, with 10,000 cases per year in western Europe and approximately 1,500 cases per year in the United States [4, 5]. Although malaria is a preventable and treatable disease, controlling and eradicating the disease remain elusive goals.

Malaria has protean manifestations, from fever with nonspecific symptoms to life-threatening complications including acute respiratory distress syndrome (ARDS) [6–8]. Traditionally, *P. falciparum* was considered the causative agent for all forms of severe malaria [6]. Over the last two decades, multiple case reports and

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series have been published in which *P. vivax*—once considered benign—had infected patients who had severe, life-threatening complications including ARDS [9–15]. Initially, severe malaria due to vivax was believed to result from a mixed *Plasmodium* infection, with the severe manifestations caused by *P. falciparum*. There is now sufficient evidence that infection with *P. vivax* alone can cause severe malarial manifestations [17]. There are also reports of *P. ovale* [17, 18], *P. malariae* [19], and *P. knowlesi* [2, 20] causing a severe form of the disease including ARDS. In recent years, there has been a paradigm shift in the presentation of severe malaria. Multi-organ failure (including renal failure, hepatic failure, and ARDS) is being increasingly reported, unlike earlier presentations of severe malaria [16, 21–24].

Noninvasive ventilation (NIV) is the delivery of positive-pressure ventilation without an endotracheal airway to patients with acute respiratory failure. It is usually administered through a tight-fitting oronasal mask (less often nasally or with a full-face mask or helmet). It has revolutionized the management of patients with acute respiratory failure [25] and is considered the modality of choice during acute exacerbations of chronic obstructive pulmonary disease [26]. It is also used in patients with acute hypoxemic respiratory failure (AHRF), most commonly in those with cardiogenic pulmonary edema and in immunocompromised patients [27]. NIV traditionally encompasses two modalities: (1) continuous positive airway pressure (CPAP), where constant pressure is provided throughout the respiratory cycle; (2) bilevel positive airway pressure (BIPAP), where a higher inspiratory positive airway pressure (IPAP) is provided during inspiration and a lower expiratory positive airway pressure (EPAP) during expiration. The role of NIV in ARDS is unclear, but it assumes importance in resource-constrained settings where the availability of invasive ventilation may not be readily available. In these situations, judicious use of NIV may be life-saving. In fact, there are reports of the use of NIV for unconventional indications, such as tuberculosis- and malaria-induced ARDS [14, 28].

We systematically review the literature on the prevalence of ARDS secondary to malaria and the role of NIV in patients with malarial ARDS.

12.2 Methodology

We searched the PubMed database using the following search terms: ("plasmodium"[ti] *or* "malaria"[ti] *or* "P. vivax"[ti] *or* "P. falciparum"[ti]) *and* ("ards"[ti] OR "ali"[ti] *or* "lung injury"[ti] or "acute respiratory distress syndrome"[ti] *or* "acute lung injury"[ti] *or* "respiratory failure"[ti]); ("plasmodium" *or* "malaria" *or* "P. vivax" *or* "P. falciparum") *and* ("ards" *or* "ali" *or* "lung injury" *or* "acute respiratory distress syndrome" *or* "acute lung injury" *or* "respiratory failure"); ("noninvasive ventilation" *or* "non-invasive ventilation" *or* "cpap" *or* "continuous positive airway pressure" *or* "nippv" *or* "noninvasive positive pressure ventilation" *or* "nipsv" *or* "noninvasive pressure support ventilation" *or* "non-invasive positive pressure ventilation" *or* "non-invasive pressure support ventilation" *or* "bipap" *or* "bilevel positive airway pressure" *or* "niv") *and* ("plasmodium" or "malaria"). We also reviewed the reference lists of primary studies, reviews, and editorials. We reviewed our personal files as well.

Table 12.1 Definitions for ARDS

AECC criteria
Onset: acute
Oxygenation: $PaO_2/FiO_2 < 200$ mmHg regardless of PEEP level; patients with PaO_2/FiO_2 scores between 200 and 300 were classified as having acute lung injury (ALI)
Chest radiograph: bilateral infiltrates seen on frontal chest radiograph
Pulmonary artery wedge pressure <18 mmHg when measured or no clinical evidence of left atrial hypertension
Berlin definition
Timing: within 1 week of a known clinical insult or new or worsening respiratory symptoms
Oxygenation: mild: 200 mmHg $< PaO_2/FiO_2 \leq 300$ mmHg with PEEP or CPAP ≥ 5 cmH_2O; moderate: 100 mmHg $< PaO_2/FiO_2 \leq 200$ mmHg with PEEP ≥ 5 cmH_2O; severe $PaO_2/FiO_2 < 100$ mmHg with PEEP ≥ 5 cmH_2O
Imaging: bilateral opacities, not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema: not fully explained by cardiac failure or fluid overload. Echocardiography may be done to exclude hydrostatic edema if no risk factor present

AECC American-European Consensus Conference, *ARDS* acute respiratory distress syndrome, *FiO_2* fraction of inspired oxygen, *PaO_2* partial pressure of arterial oxygen, *PEEP* positive end-expiratory pressure

12.3 Definition of ARDS

Acute respiratory distress syndrome was first described in 1967 by Ashbaugh et al. [29]. It is acute-onset hypoxemic respiratory failure. ARDS is diagnosed based on the presence of bilateral fluffy pulmonary opacities on a chest radiograph in the absence of left heart failure. The American-European Consensus Conference (AECC) diagnostic criteria (Table 12.1) were widely used for clinical and research purposes in defining acute lung injury (ALI)/ARDS [30]. Recently, a new definition for ARDS—the Berlin definition—has replaced the AECC criteria (Table 12.1) [31]. Irrespective of the cause, the overall 28-day ARDS-related mortality rates found by recent randomized trials ranged from 25 to 30 %. Community surveys have reported the range to be 35–40 % [32, 33].

12.4 ARDS in Patients with Severe Malaria

ARDS is a life-threatening manifestation of malaria irrespective of the causative species. It is always lethal if not treated early and appropriately. It may occur as a predominant manifestation but is usually part of multi-organ failure [34]. The onset of ARDS is usually abrupt and rapidly progressive. ARDS may occur at presentation or following treatment despite a decline in parasitemia [34, 35]. In a prospective study, 28 of 301 patients with severe malaria had ARDS at presentation; 33 developed ARDS within 48 h and 36 after 48 h [35]. All malarial patients present with dyspnea and cough that continues to worsen. Physical examination reveals tachypnea, cyanosis, use of accessory respiratory muscles, crackles, and wheezing. Hypoxia-related confusion or agitation may be present [36].

The exact prevalence of ARDS in patients with severe malaria is underestimated because of the lack of data from areas where the disease is highly prevalent. The World Health Organization epidemiological criteria of severe malaria with lung involvement include tachypnea with a respiratory rate >32 breaths/min and use of accessory respiratory muscles. However, these criteria cannot be used to diagnose ARDS because of the lack of specificity, and the fact that the prevalence would be overestimated. On reviewing only studies that utilized the AECC definition of ARDS, the prevalence of ARDS in cases of severe *P. falciparum* malaria ranged from 2.1 to 37.5 % in adults and was 1.7 % in children (Table 12.2). Likewise, the prevalence of *P. vivax*-related ARDS was 1.3–10.0 % in adults and 12.5 % in children. The prevalence of ARDS in patients with severe *P. knowlesi* malaria was 59 %, which is much higher than that due to *P. falciparum* or *P. vivax* but its accuracy is limited because of being reported in a single study (Table 12.2). The development of ALI/ARDS carries a grave prognosis with very high mortality in developing countries compared to that in developed countries (Tables 12.2 and 12.3). Timely intervention is associated with improved chances of survival [37].

The pathogenesis of malarial ARDS is not fully understood, and is thought to be the result of multiple, interrelated factors. In falciparum malaria, the development of ARDS has been attributed to sequestration of parasitized red blood cells (RBCs) in capillaries. The sequestration is due to expression of adhesion molecules on endothelial cells, which facilitates cytoadherence, resulting in blockade of the microcirculation and subsequent end-organ failure [38]. The inflammatory cascade may also be triggered with recruitment of neutrophils, macrophages, and monocytes into the lungs and release of inflammatory cytokines that cause ARDS [33]. ARDS may also develop following treatment even when the parasitemia is declining. This form of ARDS is believed to be secondary to inflammatory effects of parasitic products such as malarial hemozoin pigment, which can remain adherent to endothelial cells or may be phagocytosed by leukocytes. Concomitant bacterial co-infection of the lungs or aspiration may also contribute to the occurrence of ARDS [36].

The pathogenesis of ARDS in vivax malaria also remains unclear. It was earlier thought that *P. vivax* is incapable of cytoadherence and microvascular sequestration—and therefore unable to cause organ dysfunction. Data now suggest, however, that *P. vivax*-infected RBCs may adhere to the endothelial cell ligand chondroitin sulfate A in vitro, although not in vivo [39, 40]. Chondroitin sulfate A is abundantly expressed in the human placenta and by endothelial cells in the lung and brain, which may explain the occurrence of ALI/ARDS and cerebral malaria in patients with vivax malaria [13, 41]. The inflammatory response is greater in patients with vivax malaria than in those with falciparum malaria (plasma cytokine levels are higher in vivax malaria) [42, 43]. This also explains the lower pyrogenic threshold (level of parasitemia that causes fever) with vivax (versus falciparum) malaria [44]. In a prospective study, Anstey et al. found that *P. vivax*-infected erythrocytes may be sequestered in the pulmonary microvasculature and that there was progressive alveolar–capillary dysfunction after treatment of vivax (but not falciparum) malaria [44]. This finding is consistent with a greater inflammatory response to a given parasite burden in *P. vivax*- compared to *P. falciparum*-infested patients [44].

Table 12.2 Prevalence of acute respiratory distress syndrome in patients with severe falciparum malaria

Study	Year	Study design	Place of study	Denominator used	Patients	No. of patients	Prevalence of ARDS	Ventilatory strategy (IV or NIV)	Respiratory death
Santos et al. [73]	2012	Retrospective (1990–2011)	Portugal	Severe imported malaria in ICU	Mostly adults	59	22 (37.2 %)[a]	IV[b]	8 (36.4 %)
Patil [74]	2012	Retrospective (2011)	India	Complicated falciparum malaria	Adults	47	5 (10.6 %)	IV	3 (60 %)
Patil [75]	2012	Retrospective (2010)	India	Complicated falciparum malaria	Adults	73	5 (6.8 %)	IV	4 (80 %)
Nayak et al. [76]	2011	Prospective (2007–2009)	India	Pulmonary manifestations in severe malaria	Adults	200 (80 falciparum, 40 mixed)	10/120 (8.3 %)	NM	14 (100 %)
Dube et al. [77]	2011	Prospective	India	Severe falciparum malaria in ICU	Adults	34	4 (11.7 %)	IV	3 (75 %)
Bruneel et al. [70]	2010	Retrospective (2000–2006)	France	Severe imported falciparum malaria	Adults	400	76 (19 %)	NIV + IV	10 (7.6 %)
Sahu et al. [78]	2010	Retrospective (1998–2008)	India	Severe falciparum malaria in ICU	Adults	301	23 (7.6 %)[a]	NM	12 (52.2 %)
Phu et al. [79]	2010	RCT (1996–2003)	Vietnam	Severe falciparum malaria	Adults	370	23 (6.2 %)[a]	NM	8 (34.7 %)
Kochar et al. [80]	2010	Prospective (2007–2008)	India	Severe malaria in children	Children	150 (79 falciparum, 6 mixed)	2/85 (2.4 %)	NM	NA
Schwake et al. [37]	2008	Retrospective (1996–2003)	Germany	Imported falciparum malaria	Adults	34	4 (11.7 %)[a]	NIV + IV	0 (0 %)
Gérardin et al. [81]	2007	Retrospective (1996–2000)	Senegal	Severe falciparum malaria requiring mechanical ventilation	Children	502	9 (1.7 %)	IV[C]	2 (22.2 %)

(continued)

Table 12.2 (continued)

Study	Year	Study design	Place of study	Denominator used	Patients	No. of patients	Prevalence of ARDS	Ventilatory strategy (IV or NIV)	Respiratory death
Mohapatra [34]	2006	Prospective (1996–2002)	India	Natural history of complicated falciparum malaria	Adults	608	28 (4.6 %)[a]	NM	26 (92.8 %)
Kocher et al. [21]	2006	Prospective (2001)	India	Severe falciparum malaria in ward	Adults	192	4 (2.1 %)[a]	NM	NA
Mengistu and Diro [82]	2006	Retrospective (1998–2004)	Ethiopia	Treatment outcome in severe malaria	Mostly adults	408	30 (7.3 %)	NM	24 (80 %)
Mishra and Ray [83]	2005	Prospective	India	Pulmonary manifestations in severe malaria	Adults	150 (vivax 72, 24 mixed, 54 falciparum)	7/54 (12.9 %)	IV	4 (57.1 %)
Koh et al. [84]	2004	Retrospective (1996–2001)	Malaysia	Malaria infections in ICU	Mostly adults	31	10 (32.2 %) [ALI 2; ARDS 8]	IV	NA
Krishnan and Karnad [35]	2003	Prospective	India	Severe falciparum malaria in ICU	Adults	301	79 (26.2 %)[d]	IV[b]	70 (89 %)
Bruneel et al. [85]	2003	Retrospective (1988–1999)	France	Severe imported *P. falciparum* in ICU	Adults	93	14(15 %) [ALI 2; ARDS 12]	IV	5 (35.7 %)
Newton et al. [86]	2003	RCT (1994–2001)	Thailand	Severe falciparum malaria	Adults	100	9(9 %)[a]	IV	8 (88.8 %)
Mohanty et al. [87]	2003	Retrospective (1995–1998)	India	Severe falciparum malaria	Adult and children	608 (156 adults, 452 children)	45 (7.4 %)[a] 41 (9.1 %) 4 (2.5 %)	NM	NA
Losert et al. [88]	2000	Retrospective (1992–1999)	Austria	Severe falciparum malaria in ICU	Adults	69	4 (5.8 %)	IV	3 (75 %)
Kocher et al. [89]	1997	Retrospective (1994)	India	Severe falciparum malaria	Adults	532	16 (3 %)[a]	NM	13 (85.25 %)

Banzal et al. [90]	1999	Retrospective (1995–1997)	Saudi Arabia	Clinical patterns and complications of severe malaria	Adults and children	246	4 (1.6 %)	NM	1 (25 %)
Gachot et al. [69]	1995	Retrospective (1988–1993)	France	Severe imported *P. falciparum* malaria	Adults	40	12 (30 %) [ALI 4; ARDS 8]	NIV and IV	4 (33 %)

NM not mentioned

[a]No differentiation between cardiogenic and non-cardiogenic pulmonary edema made. ALI and ARDS based on $PaO_2/FiO_2 < 300$ and 200 respectively.

[b]All received invasive ventilation. Trial of NIV prior to intubation not mentioned.

[c]Of the 9 cases of ALI/ARDS, 4 received mechanical ventilation; there were 2 deaths

[d]18 (5.9 %) had acute lung injury (ALI) and 10 (3.3 %) had ARDS at admission with subsequent 33 patients developing ARDS within 48 h and another 36 after 48 h

Table 12.3 Prevalence of ARDS in patients with severe *P. vivax* and *P. knowlesi* malaria

Study	Year	Study design	Place of study	Denominator used	Patients	No. of patients	Prevalence of ARDS	Ventilatory strategy	Respiratory death
Lanca et al. [91]	2012	Retrospective (2004–2009)	Brazil	Severe vivax malaria in PICU	Children	24	3 (12.5 %)	Invasive ventilation	0 (0 %)
Kute et al. [92]	2012	Prospective (2010–2011)	India	Severe vivax malaria with acute kidney injury	Adults	25	4 (16 %)	Not mentioned	Not mentioned
Nayak et al. [76]	2011	Prospective (2007–2009)	India	Pulmonary manifestations in severe malaria	Adults	200 (80 vivax)	4/80 (5 %)	Not mentioned	14 (100 %)
Kochar et al. [80]	2010	Prospective (2007–2008)	India	Severe malaria in children	Children	150 (65 vivax)	1/65 (1.5 %)	Not mentioned	Not available
Kochar et al. [15]	2009	Prospective (2003–2005)	India	Severe vivax malaria admitted to classified malaria ward	Adults	40	4 (10 %)	Not mentioned	2 (50 %)
Sharma et al. [93]	2009	Retrospective (2005–2006)	India	Complications of vivax malaria	Mostly adults	221	3 (1.3 %)	Invasive ventilation	3 (100 %)
Kotwal et al. [94]	2005	Retrospective (2002)	United States (US)	Malaria in US army returning from Afghanistan	Adults	38	1 (2.6 %)	Noninvasive and invasive ventilation	0 (0 %)
Mishra and Ray [83]	2005	Prospective	India	Pulmonary manifestations in malaria	Adults	150 (vivax 72, falciparum 54, mixed 24)	0	Invasive ventilation	4 (57.1 %)
William at al.[95]	2011	Retrospective (2007–2009)	Malaysia	Severe knowlesi malaria	Adults	22	13 (59 %)	Nine invasive ventilation	6 (46.15 %)

Although some authors have linked the degree of parasitemia with ARDS [10], this is probably not always true as ARDS patients with *P. vivax* malaria have been reported to have parasite indexes as low as 0.1 % [11, 14, 45–47]. It is likely that the parasite triggers a hyperimmune response, resulting in lung injury.

Postmortem lung biopsies have revealed thickened and congested alveolar septa with patchy distribution of intra-alveolar hemorrhage and edema along with evidence of hyalinization of the alveolar membrane [48]. There is no intravascular thrombosis or lung infarction. Ultrastructural studies have revealed marked interstitial edema of the alveolar septa, swollen and narrowed capillary endothelial cells, and occlusion of alveolar septal capillaries by parasitized RBCs, leukocytes, and pigment-containing macrophages [49, 50]. Cytoadherence—the hallmark of severe falciparum malaria—is less conspicuous or even absent in vivax malaria-related ARDS [51, 52].

12.5 Noninvasive Ventilation for ARDS Patients

There are numerous advantages associated with using NIV in patients with acute respiratory failure [53], the most obvious being avoidance of intubation and its complications. This is an important consideration, especially in resource-constrained settings [54, 55]. As NIV is a high-flow system [56], the fraction of inspired oxygen can be as much as 100 % with better humidification than in rebreather masks [57]. However, it must be understood that NIV is not a replacement for invasive ventilation, and injudicious use of NIV can lead to increased mortality [58]. The success of NIV depends on appropriate selection of patients, who require close monitoring preferably in an intensive care setting (Table 12.4). Hence, NIV must be attempted only in settings where the physician has sound knowledge, the technique is indicated, and endotracheal intubation is readily available.

In physiological terms, NIV unloads the respiratory muscles, thereby decreasing the work of breathing and improving gas exchange [59]. At the same time, BIPAP provides additional comfort because of low EPAP with less feeling of suffocation. It is therefore the ideal mode for patients with all forms of acute respiratory failure. In a study evaluating the physiological effects of NIV, tidal volume was found to increase with pressure support but not with CPAP [53]. Neuromuscular drive and inspiratory muscle effort were also lower with pressure support than with CPAP [53]. In a trial evaluating CPAP, it was shown that in a subgroup of patients without acute or chronic cardiac disease the addition of CPAP did not affect endotracheal intubation or hospital mortality. It was associated with more adverse events (including four patients with cardiac arrest), which suggested a potential for harm. Hence, CPAP use cannot be recommended at present for use in ARDS patients [60].

The use of NIV for ARDS remains controversial. Most studies of NIV in patients with AHRF have been predominantly performed on those with AHRF that was cardiac-related, pneumonia-related, or had multiple etiologies including ARDS. In fact, recent studies suggested that ARDS was an independent risk factor for NIV failure [61–63]. In a systematic review, Keenan et al. demonstrated that NIV reduced

Table 12.4 Indications and contraindications for NIV in acute-care settings

Indications
Evidence of respiratory distress
Tachypnea (RR > 24/min), use of accessory muscles of respiration, paradoxical breathing
Gas exchange abnormalities
$PaCO_2 > 45$ mmHg, pH < 7.35
$PaO_2/FiO_2 < 300$
Contraindications
Absolute
Respiratory arrest
Facial deformity or trauma
Unable to fit mask
Relative
Hemodynamically unstable—shock, cardiac ischemia, or arrhythmia
Agitation, delirium, uncooperative
Bulbar palsy/weakness with poor swallow or impaired gag reflex
Unable to protect airway, poor cough reflex
Excessive secretions not managed by secretion clearance technique
Multi-organ failure
Uncontrolled copious hematemesis
Recent upper airway or upper gastrointestinal surgery
Lack of close monitoring or inexperienced personnel

the rate of intubation, shortened the intensive care unit stay, and lowered mortality in patients with AHRF [64]. However, their review included only patients with AHRF and thus cannot be extrapolated to patients with ARDS [64]. In a recent meta-analysis of 13 studies including 540 patients of ALI/ARDS, Agarwal et al. found that use of NIV was associated with a 50 % success rate in avoiding endotracheal intubation [65]. This suggests that NIV is beneficial in patients with ARDS provided the patients are carefully chosen. It is important to select patients meticulously as unselected patients (e.g., those having ARDS with shock) have uniformly poor outcomes [66]. Moreover, NIV should be applied early in the course of the disease, especially in those with mild ARDS [67]. Another important issue is early identification of patients failing NIV as delays in endotracheal intubation have been shown to be associated with decreased survival [68].

12.6 Noninvasive Ventilation for Malarial ARDS Patients

Only a few studies have evaluated the efficacy of NIV in malarial ARDS patients (Table 12.5). Of 45 cases, 39 were falciparum malaria, 7 were vivax malaria, and in 1 case the species was not mentioned. The outcome was not mentioned in five cases. Of 40 cases, 18 (45 %) failed with NIV and subsequently required intubation. The details of NIV use were mentioned in only two cases. The failure rate was

Table 12.5 Studies reporting the use of NIV in patients with respiratory failure caused by malaria

Study	Place of study	Setting	Study design	Patients	No. of patients	Type of malaria	No.	Indication of NIV	No. received NIV	Outcome	Details of NIV management
Bruneel et al. [70]	France	ICU	Retrospective	Adults	400	Severe falciparum malaria	76 (19 %) ALI 18 ARDS 58	Respiratory distress: $PaO_2 < 60$ mmHg at $FiO_2 \geq 0.21 \pm fR > 32$/min	32	Success 16 Failed 16	NA
Gera and Dhanoa [96]	India	ICU	Case report	Adults	2	Severe vivax malaria	2	ARDS	1	Failed	NA
Kasliwal et al. [97]	India	ICU	Case report	Adult	1	Severe vivax malaria	1	ARDS	1	Success	IPAP/EPAP 12/8
Schwake et al. [37]	Germany	ICU	Retrospective	Adults	34	Severe falciparum malaria	4 (11.7 %)[a]	Respiratory distress	4	NA	NA
Price et al. [13]	India	ICU	Case report	Adult	1	Severe vivax malaria	1	ALI	1	Success	CPAP 5 cmH_2O
Agarwal et al. [14]	India	ICU	Case report	Adult	1	Severe vivax malaria	1	ARDS	1	Success	IPAP/EPAP 15/5
Saleri et al. [98]	Italy	ICU	Case report	Adult	1	Severe vivax malaria	1	ALI	1	Success	NA
Kotwal et al. [94]	USA	ICU	Brief report	Adults	38	Severe vivax malaria	1	ARDS	1	Failed	NA

(continued)

Table 12.5 (continued)

Study	Place of study	Setting	Study design	Patients	No. of patients	Type of malaria	No.	Indication of NIV	No. received NIV	Outcome	Details of NIV management
Rocker et al. [99]	Canada	ICU	Prospective	Adult	1[b]	Not mentioned	1	ARDS	1	Success	BiPAP
Kalmar et al. [100]	Portugal	ICU	Case report	Adult	1	Severe vivax malaria	1	ARDS	1	Success	NA
Gachot et al. [69]	France	ICU	Retrospective (1988–1993)	Adults	40	Severe falciparum malaria	12 (30 %)	$PaO_2/FiO_2 < 300$	1	NA	CPAP

EPAP expiratory positive airway pressure, *FiO_2* fraction of O_2, *ICU* intensive care unit, *NA* not available, *IPAP* inspiratory positive airway pressure, *PaO_2* partial pressure of O_2 in arterial blood

[a]No differentiation between cardiogenic and noncardiogenic pulmonary edema made. ALI and ARDS based on $PaO_2/FiO_2 < 300$ and 200, respectively

[b]Cohort study of 10 patients with 12 episodes of ARDS with various etiologies, with one patient presenting with malarial ARDS

Table 12.6 Application of NIV in patients with ARDS

Meticulous selection of patients. Likely to benefit patients with mild ARDS early during the course.
Absence of severe hypoxemia at the outset
No major organ dysfunction [101] (e.g., acute renal failure requiring dialysis)
Absence of hypotension [66] or cardiac arrhythmias
Simplified acute physiology score (SAPS) II ≥ 34 [102]
Use of critical care ventilator with oxygen blender is preferred over portable ventilator with external oxygen supply. BIPAP mode is preferred over CPAP
Explain technique to patient because it improves compliance and adherence.
Position: patient is kept propped up at 30°–45°
Interface: Use full face mask of appropriate size. Place interface gently over face, holding it in place and start ventilation. Once patient tolerates, tighten straps just enough to avoid major leaks, avoid tightening too tight to protect from pressure ulcers
Protocol: Set pressures starting from low levels [i.e., inspiratory pressure support (IPAP) 8 cmH_2O and external PEEP (EPAP) 4 cmH_2O]. Titrate inspiratory pressure by 2 cmH_2O until expired tidal volume is ≥6 ml/kg of PBW or higher and raise PEEP by 1 cmH_2O to get SpO_2 > 92 % so the FiO_2 can be kept <0.6. Titrate FiO_2 on ventilator or add low-flow oxygen into the circuit and increase flow until SpO_2 > 92 %
Set alarms: Low pressure alarm should be above PEEP level
Monitor comfort, dyspnea, respiratory rate, heart rate, and blood pressure every 30 min for 6 h, then hourly. Continuously monitor oxygen saturation. Measure arterial blood gases at baseline, 1, 4 h, and thereafter as and when required but at least once daily
Alleviation of subjective dyspnea, fall in fR <30/min, tidal volume >6 ml/kg PBW, FiO_2 < 0.6 with increase in PaO_2/FiO_2 above baseline at IPAP ≤ 15–20/EPAP ≤ 8–10 is an optimum NIV setting for that patient
Failure to achieve the above requirements within 1–4 h must be considered failure, and patient must be intubated

BIPAP bilevel positive airway pressure, *CPAP* continuous positive airway pressure, *EPAP* expiratory positive airway pressure, *FiO_2* fraction of inspired oxygen, *IPAP* inspiratory positive airway pressure, *PBW* predicted body weight {male = 50 + [height (in) – 60] × 2.5} and {female = 45.5 + [height (in) – 60] × 2.5}, *PEEP* positive end-expiratory pressure, *SpO_2* pulse oximetric oxygen saturation

similar to that shown in a recent meta-analysis [65]. Gachot et al. first reported the use of NIV in the form of CPAP in 1 of 12 patients with ARDS caused by falciparum malaria, although the details of its use and outcome were not mentioned [69]. Agarwal et al., in 2007, reported the successful use of BIPAP in ARDS patients caused by vivax malaria and reviewed the use of NIV in three other cases of vivax-related ARDS [14]. Two of the four patients had mild ARDS. Details of NIV were available for two patients. The mean PaO_2/FiO_2 was 215, and all patients survived. In one case, CPAP was used at a pressure of 5 cmH_2O [13], and in another BIPAP was used at a pressure of 10/4 cmH_2O [14]. In the largest series on the use of NIV in malarial ARDS, 32 patients with falciparum malaria-related ARDS were treated with NIV. It successfully avoided endotracheal intubation in 16 of the 32 (50 %) patients, but the details of its use were not mentioned [70].

The use of NIV in malarial ARDS is not different from its for ARDS due to other causes. A pragmatic clinical approach would be to use NIV judiciously in patients with ARDS (Table 12.6) [27, 71]. Needless to say, facilities for establishing an

endotracheal airway should be immediately accessible. Close monitoring is required during NIV.

The following criteria indicate the need for endotracheal intubation: inability to improve or stabilize gas exchange or the appearance of dyspnea in 1 h; failure to alleviate agitation from hypoxemia or changes in mental status linked to respiratory impairment; bradycardia (heart rate <60 beats/min with altered mental status); hypotension (systolic blood pressure <90 mmHg); respiratory arrest; failure to maintain oxygen saturation ≥88 %; significant metabolic and/or respiratory acidosis (pH ≤ 7.20) [72].

Weaning the patient from NIV should be considered once the patient is stabilized, with improved oxygenation characterized by a decreased respiratory rate, alleviation of dyspnea, and decreased FiO_2 and positive end-expiratory pressure levels. The NIV duration and pressure can be reduced every 6–8 h or earlier if the patient is clinically stable. Once the respiratory rate remains at ≤35 breaths/min and the PaO_2 is ≥60 mmHg at $FiO_2 < 0.3$, NIV can be withdrawn and the patient shifted to a rebreather or an air-entrainment mask.

Key Major Recommendations

- Malaria can cause ARDS, a point that should be kept in mind when treating such patients. It may be prudent to exclude mixed infections (*P. falciparum* + *P. vivax* or mixed plasmodial + bacterial) or treat them simultaneously.
- The use of NIV in patients with malarial ARDS may be associated with good outcomes particularly when used early in the course of the disease.

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Noninvasive Ventilation in Patients with Severe Acute Respiratory Syndrome

13

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Keywords
NIV • SARS • Emerging respiratory infections

13.1 Introduction

Severe acute respiratory syndrome first emerged in Guangdong, China in November 2002 and then spread rapidly to many countries through Hong Kong in 2003 [1–4]. A 64-year-old physician from southern China, who had visited Hong Kong on February 21, 2003 and died 10 days later of severe pneumonia, is believed to have been the source of infection causing subsequent outbreaks of severe acute respiratory syndrome (SARS) in Hong Kong, Vietnam, Singapore, and Canada [1–4]. By the end of the epidemic in July 2003, there had been 8,096 cases reported in 29 countries and regions, with a mortality incidence of 774 (9.6 %) [5]. Among the 8,096 cases, 1,706 were health care workers (HCWs). A novel coronavirus (CoV) was responsible for SARS [6]. Bats are likely the natural reservoirs of SARS-like CoV [7, 8].

The clinical course of SARS generally follows a typical pattern [9]. Phase 1 (viral replication) is associated with an increasing viral load during the first week of the illness and is clinically characterized by fever, myalgia, and other systemic symptoms that generally diminish after a few days. Phase 2 (immunopathological injury) is characterized by recurrence of fever, hypoxemia, and radiological progression of pneumonia with falls in viral load during the second week of illness.

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The high morbidity associated with SARS was highlighted by the observation that even when only 12 % of the total lung field is involved by consolidation on chest radiographs, 50 % of patients require supplemental oxygen to maintain satisfactory oxygenation above 90 % [10]. Peiris et al. [9] showed peaking of the nasopharyngeal viral load on day 10 of illness followed by a progressive decrease in rates of viral shedding from the nasopharynx, in stool, and in urine from day 10 to day 21 after symptom onset in 20 patients who had serial measurements with reverse transcription-polymerase chain reaction. Thus, clinical worsening of patients with SARS during phase 2 (second week of illness) is most likely the result of immune-mediated lung injury due to an overexuberant host response rather than uncontrolled viral replication [9].

SARS spreads mainly by close person-to-person contact via droplet transmission or fomite [11]. During the global outbreak of SARS, about 20 % of patients progressed into acute respiratory distress syndrome (ARDS), necessitating invasive ventilatory support while reaching a very high viral load at the nasopharynx with the peak on day 10 of illness [9]. Thus, HCWs were particularly prone to infection while caring for patients at a close distance [1, 9, 12]. These data emphasize the need for adequate respiratory protection in addition to strict contact and droplet precautions when managing patients with pneumonia due to highly infectious diseases.

13.2 Studies Reporting Safe Application of NIV to Patients with SARS

Several uncontrolled studies have shown that single-circuit noninvasive ventilation (NIV) can be life-saving for patients in respiratory failure due to SARS infection [13–15]. Among 120 patients meeting clinical criteria for SARS who were in a hospital for infectious diseases in Beijing, 30 (25 %) had developed acute respiratory failure (ARF) at 10.7 ± 3.8 days after the onset of SARS. Among these 30 patients, 16 (53 %) exhibited hypercapnia ($PaCO_2 > 45$ mmHg), and 10 hypercapnic events occurred within 1 week of admission. NIV was instituted in 28 patients, with 1 patient intolerant of it. In the remaining 27 patients with SARS, NIV was initiated 1.2 ± 1.6 days after ARF onset. An hour of NIV therapy led to significant improvement in PaO_2/FiO_2 and a reduced respiratory rate ($p < 0.01$). Endotracheal intubation was required in one-third of the patients (9/27) despite a favorable response to NIV initially. Remarkable pulmonary barotrauma was noted in 7 of the 120 patients (5.8 %) and in 6 of those (22 %) on NIV. The overall fatality rate at 13 weeks was 6.7 % (8/120). It was higher (26.7 %) among those needing NIV. None of the HCWs contracted SARS. The authors concluded that NIV is a feasible, appropriate treatment for ARF due to SARS infection [13].

In another study, NIV was applied via oronasal mask to 20 SARS patients without chronic obstructive pulmonary disease (COPD) who had developed severe hypoxemic respiratory failure in a hospital in Hong Kong with efficient room air exchange (through timely installation of powerful exhaust fans to provide 8–12 air

changes per hour), stringent infection control measures, full personal protective equipment (PPE), and addition of a viral/bacterial filter to the exhalation port of the NIV device. The mean age of the patients was 51.4 years. The mean Acute Physiology and Chronic Health Evaluation (APACHE) II score was 5.35. SARS CoV serology was positive in 19 of 20 patients (95 %). NIV was started at a mean of 9.6 days from symptom onset. The mean duration of NIV usage was 84.3 h. Endotracheal intubation was avoided in 14 patients (70 %), in whom the ICU stay was shorter than those who required intubation (3.1 vs. 21.3 days, $p<0.001$), and the chest radiography score within 24 h of NIV was lower (15.1 vs. 22.5, $p=0.005$) compared to the intubated patients. Intubation avoidance was predicted by a marked reduction in respiratory rate (9.2 breaths per min) and supplemental oxygen requirement (3.1 L/min) within 24 h of NIV. There were no clinical infections among the 105 HCWs caring for the 20 patients receiving NIV, and 102 HCWs who had consented to blood serology testing were all negative for SARS CoV. NIV appeared effective in the treatment of ARF in the patients with SARS, and its use was safe for HCWs in this single-center study [14].

A retrospective analysis was conducted on all patients with respiratory failure identified from the Hong Kong Hospital Authority SARS Database. Intubation rate, mortality, and secondary outcome of a hospital utilizing NIV under standard infection control conditions (the same NIV hospital as described above [14]) were compared to 13 other hospitals using only invasive mechanical ventilation (IMV hospitals) [15]. The two hospital groups had comparable demographics and clinical profiles, but patients at the NIV hospital ($n=42$) had higher lactate dehydrogenase levels and worse radiographic scores on admission. Compared to the IMV hospitals ($n=451$), the NIV hospital had lower adjusted odds ratios (OR) for intubation [0.36, 95 % confidence interval (CI) 0.164–0.791, $p=0.011$] and death (0.235, 95 % CI 0.077–0.716, $p=0.011$). There was no clinical transmission of SARS among HCWs caused by the use of NIV. Compared to IMV, NIV as the initial ventilatory support for ARF in the presence of SARS appeared to be safe. Also, it is associated with a reduced need for IMV and low mortality in this study [15].

13.3 Studies Reporting Increased Risk of Transmission of SARS to HCWs via NIV

A retrospective study by Xiao et al. [16] described NIV exposure as a risk factor associated with clinical SARS infection in two HCWs in Guangzhou, China. Other risk factors included involvement in patient resuscitation and IMV [16].

The relative risk of developing SARS was 13-fold for HCWs in Toronto who were involved in intubating SARS patients versus those who were not. In contrast, NIV was not associated with a statistically significant risk for the HCWs (1/6 exposed HCWs vs. 2/28 nonexposed, risk ratio 2.33, $p=0.5$) [17]. This was probably because tracheal suctioning was not generally performed for patients ventilated with NIV, and the study sample size was small [17]. In a subsequent retrospective multi-center cohort study of more than 600 HCWs who were involved in managing

SARS patients in Toronto, their presence in the room during fiberoptic intubation (OR 2.79, $p=0.004$) or electrocardiography (OR 3.52, $p=0.002$), unprotected eye contact with secretions (OR = 7.34, $p=0.001$), patient APACHE II score ≥20 (OR 17.05, $p=0.009$), and patient PaO_2/FiO_2 ≤59 (OR 8.65, $p=0.001$) were associated with increased risk of transmission of SARS CoV [18].

In a large case–control study involving 124 medical wards in 26 hospitals in Guangzhou and Hong Kong, NIV was identified as an independent risk factor for super-spreading nosocomial outbreaks of SARS (OR 11.82, 95 % CI 1.97–70.80, $p=0.007$) [19].

A systematic review of five case–control and five retrospective cohort studies related to SARS identified four procedures that were associated with an increased risk of transmission of SARS to HCWs [20].

- Tracheal intubation [$n=4$, cohort: OR 6.6, 95 % CI 2.3–18.9; and $n=4$ case–control: OR 6.6, 95 % CI 4.1–10.6]
- NIV [$n=2$, cohort: OR 3.1, 95 % CI 1.4–6.8]
- Tracheotomy [$n=1$, case-control: OR 4.2, 95 % CI 1.5–11.5]
- Manual ventilation before intubation [$n=1$, cohort: OR 2.8, 95 % CI 1.3–6.4]

In addition, there was an influenza outbreak investigation conducted with computer fluid dynamics analysis. It described application of NIV to a patient hospitalized with hypercapnic respiratory failure due to acute exacerbation of COPD by influenza A(H3N2 virus). The patient was in a general medical ward with imbalanced airflow related to different high-efficiency particulate air (HEPA) filter settings in the ward that appeared to have converted droplets that were subjected to airborne transmission. It resulted in nosocomial infection due to the same influenza A(H3N2) virus seen in the first patient, affecting several other patients in the adjacent bay on the same ward [21].

13.4 Technical and Infection Control Considerations

Noninvasive ventilation should be commenced under strict infection control measures, as recommended in Table 13.1 for patients with SARS and other emerging respiratory infections. It is started in patients in whom nasal oxygen >5 L/min fails to maintain the target SpO_2 (93–96 %). Inspiratory positive airway pressure (IPAP) is adjusted to achieve a respiratory rate of <25 breaths per minute and exhaled tidal volumes >6 mL/kg. Expiratory positive airway pressure (EPAP) is adjusted to achieve target oxygenation with minimum carbon dioxide rebreathing. The criteria for switching to intubation include intolerance to NIV, patient fatigue, or when supplemental oxygen at 12 L/min fails to maintain at least 93 % SpO_2 while on NIV [15].

All HCWs should take precautions when managing patients with community-acquired pneumonia (CAP) of unknown etiology that is complicated by respiratory failure. Experimental studies based on a sophisticated human patient simulator and laser visualization technique have shown that the maximum exhaled air particle dispersion distance from patients receiving NIV via the ResMed Ultra Mirage mask was about 0.5 m along the exhalation port [22]. The same research group

Table 13.1 Infection control precautions in the ICU for management of SARS [15, 26]

Staff education
(a) Limit opportunities for exposure: limit aerosol generating procedures and limit number of HCWs present.
(b) Effective use of time during patient contact.
(c) How to "gown up" and "gown down" without contamination.
(d) Emphasis on importance of vigilance and adherence to all infection control measures in addition to monitoring own health.
Personal protective equipment (*PPE*)
(a) N95 respirator for airborne and surgical mask for droplet precautions.
(b) Contact precautions: Disposable gloves, gown, and cap.
(c) Eye protection with nonreusable goggles and face shield.
(d) Powered air purification respirators for use when performing high-risk procedures.
(e) No pens, paper, other personal items, or medical records allowed into or removed from the room.
(f) Immediate removal of grossly contaminated PPE and showering in nearby facility.
Environment/equipment
(a) Conform to CDC recommendation for environmental control of tuberculosis: minimum 6 air changes per hour (ACHs). Where feasible, increase to 12 ACHs or recirculate air through HEPA filter.
(b) Preferred: negative pressure isolation rooms with antechambers, with doors closed at all times.
(c) Equipment not be shared among patients.
(d) Alcohol-based hand and equipment disinfectants.
(e) Gloves, gowns, masks, and disposal units readily available.
(f) Careful, frequent cleaning of surfaces with disposable cloths and alcohol-based detergents.
(g) Use of video camera equipment or windows to monitor patients.
Transport
Avoid patient transport where possible. Balance risks and benefits of investigations that necessitate patient transport.
Special precautions for ICU
(a) Viral/bacterial filter placed in expiratory port of bag-valve mask.
(b) Two filters per ventilator: between expiratory port and the ventilator; another on the exhalation outlet of the ventilator.
(c) Closed system in-line suctioning of endotracheal/tracheostomy tubes.
(d) Heat and moisture exchanger (HME) preferred to heated humidifier. Careful handling of contaminated HME.
(e) Scavenger system for exhalation port of ventilator. Optional if negative pressure with high air exchange (>12/h) is achieved.

demonstrated that the maximum exhaled air dispersion distance from the Respironics ComfortFull 2 mask was about 1 m at a predictable direction from the exhalation diffuser perpendicular to the patient. Leakage though the Respironics Image 3 mask, connected to the whisper swivel exhalation port, was much more extensive and diffuse even at a low IPAP of 10 cmH_2O [23]. The whisper swivel is an efficient exhalation device to prevent carbon dioxide rebreathing, but it is not advisable to use such an exhalation port when managing patients with highly infectious conditions such as SARS for fear of causing major nosocomial infection. It is also important to avoid the use of high IPAP, which could lead to wider distribution of

Table 13.2 Recommendations by the European Respiratory Society and European Society of Intensive Care Medicine for use of NIV during the pandemic 2009 influenza A(H1N1) infection [27]

(a) Prudent isolation of the patient coupled to protective measures for HCWs and other patients are the keys to limiting disease transmission.
(b) Use double-circuit tubes (or special filters for nonrebreathing devices).
(c) Minimize leaks.
(d) Use full-face masks or helmets.
(e) Avoid heated humidification.
(f) Protect hospital personnel with standard measures (i.e., wearing gloves, washing hands, use of masks, "negative pressure" rooms).
(g) Discard all masks, circuits, filters, and headsets immediately and safely after use according to routine infection control procedures. Routine exterior cleaning of ventilators and replacement of external filters should be sufficient to stop the spread of infection if ventilators are used on other NIV patients with H1NI. Complete decontamination may be considered before ventilators are used for patients without H1N1.

exhaled air and substantial room contamination [23]. These data have important clinical implications regarding the prevention of any future nosocomial outbreaks of SARS and other highly infectious conditions such as pandemic influenza.

Noninvasive ventilation should be applied in patients with severe CAP only if there is adequate protection for HCWs because of the potential risk of transmission. The organisms can spread via either deliberate or accidental mask interface leakage and flow compensation causing dispersion of contaminated aerosol [24]. In patients with respiratory failure undergoing NIV via nasal masks, air leakage may occur through the mouth or routes other than the exhalation valve [25]. For example, the patient may loosen the mask strap to relieve discomfort around the nasal bridge, and air leakage from the nasal bridge is definitely a potential source for transmission of viral infection. Careful mask fitting is important for successful, safe application of NIV [24]. Addition of a viral/bacterial filter to the breathing system of NIV between the mask and the exhalation port [13–15] or using dual-circuit NIV may reduce the risk of nosocomial transmission of viral infection [22].

In view of the observation that higher ventilator pressures result in wider dispersion of exhaled air and a higher concentration of air leakage [22, 23], it is advisable to start NIV with a low IPAP level (8–10 cmH_2O), gradually increasing it as necessary. Indeed, SARS-related ARF has been reported to respond readily to low positive pressures with CPAP (4–10 cmH_2O), IPAP (<10 cmH_2O), and EPAP of (4–6 cmH_2O) [26]. Higher pressures should be avoided because of the common findings of spontaneous pneumomediastinum and pneumothorax in SARS [1, 10, 12].

During the 2009 pandemic of influenza A(H1N1)pdm09 infections, it was recommended that NIV be applied to suitable patients (e.g., those with mild to moderate acute hypercapnic respiratory failure or acute pulmonary edema or those with resolving ARDS) via a helmet mask with double-circuit tubes or a total full-face mask with filters and avoidance of heated humidification. This was in addition to prudent isolation of the patients coupled with protective measures for the HCWs and other patients (Table 13.2) [27]. The Health Protection Agency, UK, has recommended airborne precaution when applying NIV in patients with the

H1N1pdm09 infection [28]. Also, the most recent World Health Organization (WHO) interim guidance on management of the novel CoV has also recommended the use of NIV for mild cases of ARDS without hemodynamic instability [29].

The WHO interim guidelines on prevention and control of acute respiratory diseases in health care has included NIV among those aerosol-generating procedures in which there is possibly increased risk of respiratory pathogen transmission. In addition to maintaining contact, droplet, and standard precautions among HCWs when providing routine care to such patients, the WHO recommends full PPE for the HCW, covering the torso, arms, eyes, nose, and mouth. It includes a long-sleeved gown, single-use gloves, eye protection, and an N95 mask or equivalent as the minimum level of respiratory protection. NIV should be provided in an adequately ventilated single room. There should also be an expiratory port with a bacterial/viral filter that reduces aerosol emission [30].

13.5 Future Research

Emerging infectious diseases such as SARS and H1N1pdm09 are highly infectious and are associated with significant morbidity and mortality. NIV may play a limited supportive role for early ARDS/acute lung injury as a bridge to invasive mechanical ventilation in SARS and other emerging respiratory infections. It is contraindicated, however, in critically ill patients with multi-organ failure and hemodynamic instability [24, 27, 29]. As the application of NIV may potentially disperse infected aerosols [22, 23], further research is needed to examine the safety and exhaled air dispersion distances during application of NIV via mask, including the helmet, using double-circuit tubing. When we have a better understanding of these areas, HCWs can better protect themselves within the dangerous distances when managing patients with ARF due to highly infectious diseases. More research is also needed regarding technical improvements of the NIV masks and viral/bacterial filters, as well as in the design of a safer hospital ward environment, to prevent nosocomial transmission of these infections. Advances in knowledge in these research areas can facilitate management of ARF due to future SARS outbreaks and other emerging infectious diseases, such as pandemic influenza.

Key Major Recommendations

- NIV may play a supportive role for early ARDS/acute lung injury as a bridge to invasive mechanical ventilation in patients with SARS and other emerging infections, although it is contraindicated in critically ill patients with multi-organ failure and hemodynamic instability.
- In addition to strict contact and droplet precautions, HCWs should have adequate respiratory protection when managing patients with SARS as the application of NIV may disperse potentially infected aerosols.

- Further research is needed to determine the exhaled air dispersion distances and safety during application of NIV via masks (e.g., helmet masks, total full-face mask) and the use of dual circuits so health care providers can better protect themselves within dangerous areas when managing patients with ARF due to highly infectious diseases.
- More research is needed regarding technical improvements in noninvasive positive-pressure ventilation masks, viral/bacterial filters, and the design of safer hospital ward environments with adequate air changes to prevent nosocomial transmission of these infections.

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Noninvasive Ventilation in Patients with Acute Respiratory Failure Due to Influenza A(H1N1) Virus Infection

14

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Keywords
Noninvasive ventilation • Pandemic • Influenza A(H1N1) • Pneumonia

14.1 Introduction

Viruses are an age-old foe of humans and have caused great loss of life on a global scale. For example, the "Spanish flu" outbreak (1918–1919) caused 50 million deaths worldwide [1]. RNA viruses of the Family Orthomyxoviridae [2]—including the influenza A(H1N1) virus—have caused many epidemics. The virus undergoes constant genetic changes and gave rise to the new H1N1 (swine flu or type A influenza), which started the pandemic that began in Mexico in 2009.

A published series [3–7] showed that patients admitted to the intensive care unit (ICU) developed multi-organ failure, especially hypoxemia-induced acute respiratory failure (ARF). Mortality in this series ranged from 17 to 40 %. Ventilation was required in 64–100 % of the patients admitted to the ICU [3–8], whether due to hypoxemia symptoms such as adult respiratory distress syndrome (ARDS) or to exacerbation of chronic pathologies such as cardiac failure or chronic obstructive pulmonary disease (COPD), which are often accompanied by hypercapnia. The need for invasive mechanical ventilation (IMV) was considered to be one of the factors linked to hospital mortality [6]. With regard to the kind of ventilation used, this varied depending on the series [3–5, 7, 8], although IMV was more commonly used than noninvasive ventilation (NIV). Also, there was a high failure rate (>70 %) in

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Table 14.1 Outcomes of various ventilation systems and mortality rates in several series

Study	Not ventilated	IMV	NIV	NIV failure	Mortality Day 28	Mortality[a]
ANZIC [6], *n*(%) (*n* = 722)	250 (26)[b]	456 (64)[b]	NR	NR	NR	103 (14)
Estenssoro [8], *n*(%) (*n* = 337)	–	273 (81)	64 (19)	–	NR	156 (46)
Kumar [3], *n*(%) (*n* = 168)	32 (19)	81(48)	55(33)	47 (85)	24 (14)	29 (17)
Domínguez [4], *n*(%) (*n* = 58)	4 (7)	32 (55)	22 (38)	16 (72)	23 (40)	24 (41)
Rello [5], *n*(%) (*n* = 32)	8 (25)	16 (50)	8 (25)	6 (75)	NR	8 (25)
Villabón,[c] *n*(%) (*n* = 12)	–	12	0	0	NR	4 (33)
Villamagua,[c] *n*(%) (*n* = 15)	–	15	0	0	NR	6 (40)
Belenguer [10], *n*(%) (*n* = 10)	1(10) 0	2 (20) 0	7 (70) 5[d]	2 (20) 0	NR NR	1 (10) 0

n, number of patients
IMV invasive mechanical ventilation, *NIV* noninvasive ventilation, *NR* not reported
[a]Mortality on day 60 and global mortality
[b]*n* = 706
[c]Data from Colombian and Ecuatorian series published by Rodríguez et al. [7]
[d]Data corresponding to hypoxemic group

the case of NIV (Table 14.1). Given the low success rate of NIV [3], the controversial indications for using it in hypoxemic patients, and the risk of facilitating aerosol-borne spread of the virus and thus the danger to health care personnel, in 2009 scientific societies [9] made various recommendations concerning its use. One was that NIV was best applied: (1) in patients with hypercapnia-exacerbated COPD; (2) in patients whose heart diseases were accompanied by acute pulmonary edema; (3) to prevent postextubation failure. In the case of patients with acute hypoxemia and the associated risk of organ failure, prolonged NIV treatment may lead to risky intubation. Accordingly, NIV should not be used as a matter of course.

Our experience [10] produced results that differed from those in previously published studies on the use of NIV. Ten patients (2009–2010) were entered in the national register of virus influenza A(H1N1) of the Infectious Diseases Work Group of the Spanish Society of Intensive and Critical Care Medicine and Coronary Units. Seven of these patients displayed primary viral pneumonia (Table 14.2). Most of the patients were young and otherwise healthy, but excess weight (40 %) and pregnancy (two patients) were notable factors. Seven patients (7/10, 70 %) underwent NIV. Two patients were intubated on admission, and one did not require mechanical ventilation. Overall mortality was 10 % (one patient). This patient had been transferred from another hospital with multi-organ failure and died 24 h after admission. A group of five patients with hypoxemia were analyzed (Table 14.2) especially in connection with radiological signs of hypoxemia and liver failure. All patients were

Table 14.2 Baseline characteristics of comorbidity, pulmonary disease, laboratory and outcomes of patients admitted to the ICU

Parameters	Global ($n=10$)	Hypoxemic Group ($n=5$)
Sex, men ($n=10$), *n* (%)	5 (50)	3 (60)
Age, years[a]	38 (27–47)	45 (27–48)
SOFA score[a]	4 (3–6)	4 (3–4)
APACHE II score[a]	8 (7–16)	8 (6–12)
Multi-organ failure at admission, *n* (%)	1 (10)	0
Setting		
Emergency room, *n* (%)	7 (70)	4 (80)
ICU at another hospital, *n* (%)	2 (20)	
Ward, *n* (%)	1 (10)	1 (20)
Co-morbidities		
Pregnancy, *n* (%)	2 (20)	0
Hypertension, *n* (%)	1 (10)	1 (20)
Smoking, *n* (%)	1 (10)	1 (20)
Obesity, *n* (%)	4 (40)	4 (80)
Castleman disease	1 (10)	0
Pulmonar infection		
Viral primary pneumonia	7 (70)	5 (100)
Acute asthma	1 (10)	–
Ventilatory insufficiency	1 (10)	–
Drug intoxication	1 (10)	–
Opacity on initial chest radiograph, n (%)		
1/4 quadrants	3 (30)	0
2/4 quadrants	2 (20)	1 (20)
3/4 quadrants	2 (20)	2 (40)
4/4 quadrants	3 (30)	2 (40)
Laboratory tests		
Lactate dehydrogenase,[a] UI/L	934 (448–2,503)	934 (772–2,503)
Alanine aminotransferase,[a] UI/L	63 (14–76)	72 (45–406)
Leukocytes,[a] per mm^3	13,150 (4,375–18,125)	4,400 (4,150–9,750)
Platelets,[a] per mm^3	185,500 (128,750–274,500)	165,000 (131,000–238,000)
Ventilatory therapy on admission		
NIV *n* total (%)/*n* total failure (%)	7 (70)/2 (28)	5 (100)
Viral primary pneumonia	5 (71)/0	5 (100)
Acute asthma	1 (14.5)/1	0
Ventilatory insufficiency	1 (14.5)/1	0
IMV[b]	2 (20)	0
Not ventilated	1 (10)	0
Mortality, n (%)	1 (10)	0

SOFA Sequential Organ Failure Assessment, *APACHE* Acute Physiology and Chronic Health Evaluation, *ICU* intensive care unit, *NIV* noninvasive ventilation, *IMV* invasive mechanical ventilation

n number of patients

[a]Median and interquartile index 25–75, rest percentage

[b]Viral primary pneumonia (one case) and drug intoxication (one case)

treated with NIV and continuous positive airway pressure (CPAP). Orotracheal intubation was not required in any cases, and no patients died in the ICU or during the hospital stay (Tables 14.1 and 14.2). The mean interval from the onset of symptoms to ICU or hospital admission was 5 days.

Our tentative explanations for these highly satisfactory results are (1) the virtual absence of co-morbidity in a relatively young group of patients whose only adverse factors were excess weight and pregnancy (according to most series) [5–8]; (2) a low organ-failure score on the Sepsis-Related Organ Failure Assessment (SOFA) scale—on which hypoxemic respiratory failure was the most salient problem—compared with the scores in other series [3–5, 7]; (3) the heightened awareness of health personnel, who had received health-authority guidelines to the effect that patients with pulmonary infiltrates and significant hypoxemia were to be admitted to the ICU straightaway to receive assisted ventilation. That is why our intervals to ICU admission are similar or lower than those in previously published studies [3, 4, 7] given that, with one exception, the patients were not placed in wards first. Similar to our results, the Argentina series [8] showed that 64 patients were treated with NIV to good effect. In that case, NIV boosted patient survival (24 % vs. 13 %, $p = 0.02$). These data support the idea that greater use of NIV might have reduced the need for IMV and quite possibly the mortality rate, but this is of course no more than a supposition.

There are considerable disparities in the way NIV is used, but the published series [3–7] show a high failure rate. By contrast, our results [10] showed successful NIV-based treatment. We therefore recommend early NIV/CPAP treatment for at least a few hours in young patients with pneumonia-induced hypoxemia caused by type A influenza and where no organ failure is apparent on the SOFA scale. This does not mean that NIV is an alternative to IMV but, rather, that clinically well-placed patients may benefit from NIV for treating ARF. If there is no improvement or the patient suffers from organ dysfunction, it is best to proceed with orotracheal intubation to prevent death—a course of action recommended in one series [5], where there was a higher mortality rate among patients in which NIV failed than among those who had been intubated from the outset.

Key Recommendations

- Patients affected by virus influenza A(H1N1) and displaying multi-organ failure (respiratory, renal, hemodynamic, hepatic) should be admitted to the ICU.
- Most patients with pulmonary infiltrates and ARF should undergo mechanical ventilation in an ICU, with the option of round-the-clock invasive or noninvasive assisted ventilation.
- Invasive mechanical ventilation is “the gold standard” for treating ARF.
- Early application of NIV can be recommended for young patients with organ failure as measured by the SOFA scale where hypoxemic ARF is the main problem.

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15 Ventilatory Strategy Used for Management of Acute Respiratory Failure Due to Novel Influenza A(H1N1) Infection

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Keywords
Noninvasive mechanical ventilation • Acute hypoxemic respiratory failure • Influenza A(H1N1) • Average volume assured pressure support

15.1 Brief History of Novel Pandemic Influenza A H1N1

The first cases of the novel influenza A(H1N1) virus were reported in April 2009, especially in Mexico and the United States [1, 2]. The disease spread rapidly, becoming a pandemic by June 2009. On August 21, 2009, a total of 177 reported cases of novel influenza 182.166 A(H1N1) infection, of which 1,799 were fatal [2]. It has been observed in animal studies that the novel influenza virus A has a high replication rate in lung tissue, with a great capacity to invade the lower respiratory tract in humans, causing especially acute fulminant respiratory failure.

The acute respiratory failure (ARF) in patients with novel H1N1 disease—its most severe form of presentation—includes diffuse pulmonary infiltrates and severely compromised oxygenation. The alveolar-arterial gradient of oxygen is also compromised once the acute respiratory syndrome (ARDS) is established.

Studies on the management of patients with ARF and infection with novel H1N1 influenza are based on the most severe form of respiratory failure, multiple pulmonary infiltrates, $PaO_2/FiO_2 > 200$, and even severe multiple organ damage.

Novel H1N1 influenza infection is a disease whose lethality is based on the presence of progressive ARF for 48–72 h after presentation of the disease. Hence, there is a period during which the disease is becoming established and therefore when early intervention could halt its progression, thereby reducing its morbidity and mortality.

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15.2 Ventilatory Strategies to Combat Acute Respiratory Failure (Nonhypoxemic Patients)

Although the lethal form is the appearance of refractory hypoxemic ARF infection, novel influenza A(H1N1) can present as ARF due to exacerbation of a chronic respiratory lung disease [e.g., asthma, chronic obstructive pulmonary disease (COPD)], other chronic respiratory diseases, bacterial pneumonia secondary to infection with novel influenza A(H1N1), or viral pneumonitis [3].

The European Respiratory Society (ERS) and the European Society of Intensive Care Medicine (ESICM) stated that noninvasive mechanical ventilation (NIMV) [4] should not be considered a treatment for hypoxemic ARF secondary to a pandemic and likely to progress to ARDS. The main reasons NIMV should not be considered the first line of treatment are the following: (1) It has poor clinical efficacy regarding severe ARF that rapidly progresses to ARDS. (2) Patients infected with the novel influenza A(H1N1) virus have more heterogeneous hypoxemic ARF than patients with hypercapnic respiratory failure. (3) Aerosol particles released by NIMV expand and spread the infection.

The use of NIMV can be justified, however, to avoid endotracheal intubation in certain cases. The types of the ARF for which NIMV can be prescribed are in patients who are experiencing exacerbation of chronic respiratory lung diseases, such as asthma or COPD, and other chronic respiratory disease, bacterial pneumonia secondary to infection with novel influenza A(H1N1), and mild viral pneumonitis ($PaO_2/FiO_2 > 200$).

Hajjar et al. [5] treated five patients (62.5 %) who required invasive mechanical ventilation during the first 24 h after ICU admission. NIMV was useful in three of the patients (37.5 %), each of whom had a mild form of the disease assessed by computed tomography. Estenssoro et al. [6] used NIMV in 64 patients (19 %) with good results in patients with mild to moderate disease.

Briones Claudett et al. [7] reported two patients who required noninvasive ventilation (NIV) with favorable results. NIMV was initiated using bilevel positive airway pressure (BIPAP) mode S/T (spontaneous/timed) with a respiratory rate of 15. It had a programmed tidal volume (Vt) of 200 ml exhaled for a 42-kg patient and 300 ml for a 60-kg patient, each infected with influenza A novel associated H1N1 and chronic lung disease. The average volume-assured pressure support (AVAPS) ventilatory strategy was useful in patients with COPD exacerbation, infection, asthma, and those with mild forms of novel influenza A(H1N1) infection. The S/T-BIPAP + AVAPS ventilation strategy allows a fixed preset tidal volume that is maintained constant under inspiratory pressure variations. (BiPAP S/T) with average volume assured pressure support (AVAPS) allows for setting a fixed tidal volume, and the system output automatically adjusts based on variations in inspiratory pressure to ensure the predetermined target value. The initial ventilatory parameters must be programmed in mode BIPAP-S/T + AVAPS with an inspiratory pressure (IPAP) of 18–26 cmH_2O and a minimum of 12 applications scheduled as well as positive expiratory pressure (EPAP) of 6–8 cmH_2O for a programmed tidal volume corresponding to 45.5 + 0.91 (height in cmt – 152.4). 8–10 ml/kg body weight per patient. Were given supplements O_2 via an adapter circuit close to the facemask in order to maintain SaO_2 above 94 % (Fig. 15.1).

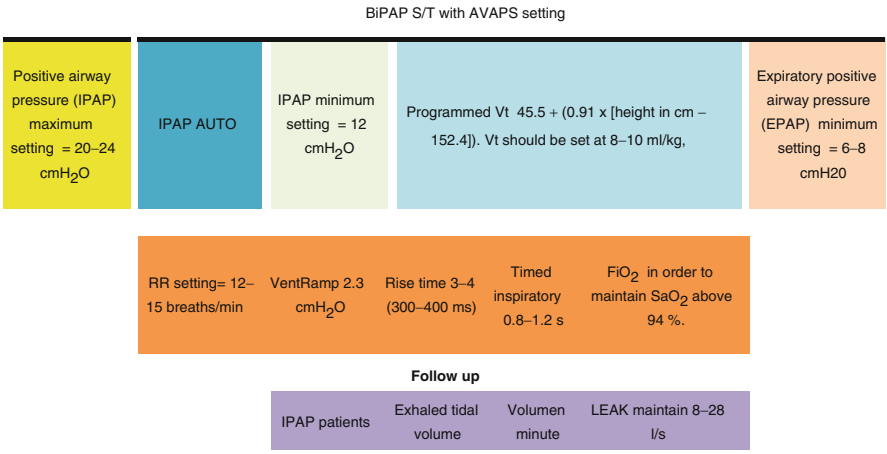

Fig. 15.1 Ventilatory strategy with BiPAP S/T and average volume assured pressure support (AVAPS)

Table 15.1 Use of noninvasive mechanical ventilation in the presence of influenza virus A(H1N1) infection

(a) Reserve noninvasive mechanical ventilation (NIMV) for patients with acute respiratory distress syndrome without severe criteria.
(b) Perform NIMV preferably in negative-pressure rooms.
(c) Preferably use respirators with dual circuits.
(d) Use accessory airways safely (e.g., masks that cover the entire face).
(e) Practice strict compliance with all security measures for staff (air insulation).
(f) Never undertake invasive mechanical ventilation in the emergency room or shared rooms.

15.3 Noninvasive Ventilation Strategies in Hypoxemic Patients

The Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias (SEMICYUC) drew up recommendations regarding the use of NIV during the pandemic that followed the 2010–2011 epidemic. It stated that it is not advisable to use noninvasive ventilation in patients who require respiratory support where there is high suspicion of infection with the new influenza virus A(H1N1) [8]. The reason for this recommendation is the risk of its generating aerosols, which increase the risk of transmission to health care workers. Also, it usually contributes to a poor clinical outcome in these patients. Before deciding to use NIMV, the risk-benefit ratio should be assessed, especially considering certain aspects, shown in Table 15.1.

The ERS/ESICM recommend avoiding NIMV. Instead, they recommend intubating patients infected with the new H1N1 virus who have been admitted to an intensive care unit (ICU) with severe hypoxemia that rapidly develops into ARDS, multiple organ failure, and refractory hypoxemia. NIMV should be considered only

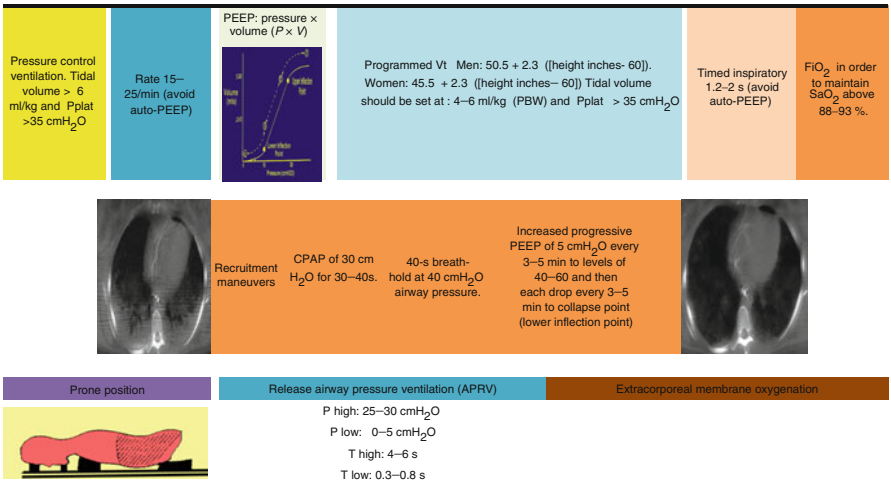

Fig. 15.2 "Open lung" management of ARDS

for patients with moderate hypercapnic ARF secondary to exacerbation of a chronic respiratory disorder, ARF secondary to acute pulmonary edema, or ARF after extubation secondary to ARDS due to H1N1 virus infection. (Fig. 15.2).

There are some reports in the literature of using NIMV in patients with novel influenza A(H1N1) infection. Winck and Marinho [9] described a 53-year-old patient who underwent NIV (BiPAP Vision; Philips Respironics, Murrysville, PA, USA) with an orofacial mask in a bilevel mode with inspiratory pressure (IPAP) of 16 cmH_2O and expiratory pressure in the airway (EPAP) of 8 cmH_2O that was initiated and then switched to continuous positive pressure airway (CPAP) of 10 cmH_2O with FiO_2 at 25 %. After 1 h, the PaO_2/FiO_2 increased to 364, and CPAP was discontinued 12 h later.

Djibré et al. [10] reported a case of a 38-year-old woman at 31 weeks' gestation who underwent continuous NIMV for 72 h through a face mask with an FiO_2 of 100 %, IPAP of 14 cmH_2O, and EPAP of 5 cmH_2O.

Rello et al. [3] reported that after 3 days of intermittent NIMV 6 (75 %) of the 8 (33.3 %) patients who underwent NIMV required intubation and IMV. Two of them (33 %) died anyway. The SOFA score at hospital admission in the patients who failed NIMV (8.1 ± 2.3) was higher than that in those who responded to the NIMV (2.5 ± 0.7) ($p = 0.01$).

Miller et al. [11] reported 13 patients on NIMV, but 11 of them were intubated within a median of 7.9 (IQR 2.8–20.8) hours. Krumar et al. [12] reported 136 patients (81.0 %) who were mechanically ventilated the first day of ICU admission. Among them, 128 (76.2 %) underwent IMV and 55 (32.7 %) NIMV. In all, 47 of the NIMV patients (85.4 %) were switched to IMV. There was another report of a small number of patients, with 5 of the 10 patients having pneumonia and hypoxemic failure. NIMV was 100 % effective in terms of improving oxygenation and avoiding

intubation. It should be noted, however, that these patients had only respiratory failure when starting the NIMV, with no other organs compromised [23].

For patients who present with severe disease, it is prudent to perform early intubation and/or admission to the ICU given the rapid progression in these cases. NIMV has little success here. During the pandemic it was reported that NIMV was used in 25–45 % of patients, with a 75 % failure rate [3, 12, 13].

In the Canadian experience, approximately 30 % of patients were admitted to the ICU and underwent NIMV. Altogether, 85 % of them required subsequent intubation and invasive ventilation. Given the high failure rate and duration of ventilatory support, routine use of NIMV in patients with H1N1 should be avoided. The reasons for failure of NIMV in this population may be that the patients almost uniformly present with hypoxemic respiratory failure and normal $PaCO_2$. Furthermore, improvement and resolution of H1N1 pneumonitis is generally slow, so NIVM may be less useful.

Patients' ventilation should be managed with a protective strategy: low tidal volumes (target 6 ml/kg) [14], opening strategy lung ventilation with PEEP adjusted based on the FiO_2 to a plateau pressure of 30–35 cmH_2O and SpO_2 of 88–90 % (ARDS Network protocol) [24]. Amato [15] showed how using lower tidal volume and higher PEEP reduced mortality by 33 % (NNT = 3). The ARIES study NETWORK of Jesus Villar et al. [14] reported similar results.

Three studies addressed the use of high levels of PEEP with low tidal volume: EXPRESS, LOVs, and ALVEOLI [16–18]. In the LOVS study, the authors compared 10 vs. 16 cmH_2O of PEEP in patients who had low tidal volume. Amato et al.'s patient group was employed as the controls. The EXPRESS study employed the ARDS Network protocol control group and compared PEEP levels of 7 vs. 15 cmH_2O. Mortality was similar in the three studies. In the ALVEOLI study clinical outcomes were similar whether lower or higher PEEP levels were used. A recent meta-analysis [19] examined three trials involving 2,299 patients and demonstrated that high PEEP levels was not associated with improved hospital survival. This protective ventilatory strategy has traditionally been associated with reduced mortality. It should be noted, however, that several recent meta-analyses of randomized trials using ventilatory strategies to protect the tidal volume in the lungs demonstrated that it is not the most important parameter. They concluded that the driving pressure is the difference between the plateau pressure and PEEP during controlled ventilation, which is therefore the most important parameter to optimize [20].

Amato et al. demonstrated reduced mortality using recruitment maneuvers (CPAP 40 cmH_2O). Borges et al. [21] used a technique aimed at achieving 95 % lung recruitment. Its success was confirmed by blood gas tomographic studies. The aim of recruitment maneuvers is to achieve and maintain effective lung reexpansion over time by selecting an appropriate level of PEEP.

A prospective cohort study in Ecuador included 24 ARDS patients. It was highly suspected that the ARDS was caused by influenza A(H1N1) [22]. The patients had a mean PaO_2/FiO_2 of 112 ± 34 and a mean APACHE II score of 18.83 ± 5.1. The patients were treated using maximizing recruitment maneuvers. The reported ICU mortality was 16.6 %.

Alternative modes of ventilation—placing the patient in a prone position or applying high-frequency oscillatory ventilation, release airway pressure ventilation (APRV), or high-frequency ventilation (HFV)—may improve oxygenation in intubated patients. APRV is a time-triggered, pressure-cycled ventilation mode that allows spontaneous breaths throughout the respiratory cycle. It has been widely used in patients with ARDS and has been observed to improve oxygenation. It also reduces the need for sedation and paralysis. During APRV, pressure in the airway is scheduled on two levels called P_{high} and P_{low} and into two periods called T_{high} and T_{low}. They are analogous to inspiratory pressure, PEEP, inspiratory time, and expiratory time, respectively. There are no conclusive data pertaining to whether APRV improves or worsens the results in patients with lung injury, particularly because the combination of pressure and the controlled mode can produce unpredictable spontaneous breaths and tidal volumes. It is known that high tidal volumes are associated with worse ARDS outcomes [24].

Sundar et al. [25] found that 11 of 14 patients had refractory hypoxemia despite APRV application. However, by combining the use of APRV with placing the patient in a prone position reduced mortality by 27.3 % (3/11). The authors concluded that the prone position combined with APRV improves oxygenation and limits organ dysfunction in patients with ARDS due to novel influenza A(H1N1).

The Spanish Working Group on Influenza A (SEMICYUC) noted that 75–90 % of patients who require mechanical ventilation and had severe hypoxemia require rescue treatment how: inhaled nitric oxide, high-frequency ventilation, or membrane oxygenation by extracorporeal circulation.

Administration of inhaled nitric oxide, high-frequency ventilation, or membrane oxygenation by extracorporeal circulation [26, 27] are still controversial.

Conclusion

Various techniques can be used clinically in strategies to address ARF due to novel influenza infection A(H1N1). NIMV should be reserved for special cases. The risk-benefit ratio regarding use of NIMV should be carefully evaluated. NIMV should not be used in patients with moderate to severe ARDS. Ventilation strategies using both noninvasive strategies (BIPAP S/T or BiPAP S/T + AVAPS) and invasive strategies (protective ventilation strategy with recruitment maneuvers, APRV) have proven useful in various clinical scenarios.

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Noninvasive Mechanical Ventilation in Patients with Acute Respiratory Failure Due to Pandemic Influenza A(H1N1) Virus

16

S. Egbert Pravinkumar

Keywords
Respiratory Failure • Pandemic H1N1 influenza • Non-invasive ventilation

16.1 Introduction

Pandemic influenza A (PA-H1N1) is a new strain of influenza virus that was first identified in Mexico and United States during the early part of 2009. The PA-H1N1 virus originated from the swine influenza (H1) virus circulating in North American pigs.

Animal studies have shown that the novel influenza virus caused increased morbidity and replicated to high titers in lung tissue, explaining its pathogenicity and capacity to invade the lower respiratory tract in humans and resulting in rapid and fulminant respiratory failure.

About 30–40 % of severe cases globally have occurred in previously healthy children and adults, usually under the age of 50 years. Patients with severe disease present with fever, cough, dyspnea, respiratory distress, increased serum lactate dehydrogenase levels, and bilateral patchy pneumonia and infiltrates [1]. Respiratory presentations of H1N1 virus infection include viral pneumonitis, exacerbations of asthma or chronic obstructive pulmonary disease (COPD), exacerbations of other underlying disease, secondary bacterial pneumonia, and croup/bronchiolitis in the pediatric population [2].

Clinical deterioration is characterized by sudden, rapidly progressive respiratory failure with persistent, refractory hypoxia, bilateral diffuse pulmonary infiltrates, and low PaO_2/FiO_2 meeting the criteria for acute respiratory distress syndrome (ARDS). Severe respiratory failure is common during the first week, with the

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incidence decreasing as the week progresses. Refractory hypoxia was the major cause of death, followed by multi-organ failure and shock. Shock was more significant during the latter part of the disease course. Other organ failures are seen in the kidneys, liver, and bone marrow.

During the epidemic about 10–30 % of hospitalized patients needed intensive care unit (ICU) admission. Co-morbidities were noted in 32–84 % of patients admitted to the ICU. They include obesity, COPD, diabetes mellitus, asthma, immunosuppression, chronic kidney disease, and heart failure.

The overall ICU mortality rate for critically ill patients with PA-H1N1 was close to 17 % [1]. Factors independently associated with mortality included the requirement for invasive mechanical ventilation (IMV) and a low PaO_2/FiO_2 at ICU admission, the presence of co-morbidities, and older age. Autopsy findings showed three distinct pulmonary pathologies: diffuse alveolar damage (DAD), necrotizing bronchiolitis, and DAD with alveolar hemorrhage.

16.2 Ventilatory Management

Invasive mechanical ventilation with a lung-protective ventilatory strategy and fluid restriction is recommended as the initial approach for managing patients with pandemic A(H1N1) infection complicated by ARDS.

Noninvasive mechanical ventilation (NIMV) has been used as first-line therapy in a small number of patients. Most of them deteriorated and subsequently needed IMV. The guidelines endorsed by the European Respiratory Society (ERS) and European Society of Intensive Care Medicine (ESICM) state that NIMV should not be considered an alternative to IMV in patients with acute hypoxemic respiratory failure secondary to PA-H1N1 infection that is likely to progress to ARDS [3]. The reasons against NIMV being used as first-line therapy in PA-H1N1-associated respiratory failure are as follows:

- Poor clinical efficacy in severe respiratory failure that rapidly progresses to refractory hypoxemia and ARDS
- Patients with PA-H1N1 present almost uniformly with hypoxemic respiratory failure, not hypercapnic respiratory failure
- Great concern about aerosol droplet particle dispersion and spread of infection

Indications for NIMV in patients with PA-H1N1 infection are the following:

- During the early stages with mild respiratory failure characterized by minimal pulmonary infiltrates and $PaO_2/FiO_2 > 250$
- Mild to moderate hypercapnic respiratory failure such as exacerbation of COPD related to PA-H1N1 infection
- Postextubation respiratory failure due to resolving ARDS
- Weaning from prolonged mechanical ventilation
- Patients with cardiogenic edema in the absence of pneumonia, multi-organ failure, and refractory hypoxemia

There are some additional requirements for NIMV.

- Negative-pressure or well-ventilated rooms
- Bacterial and viral filters in the expiratory circuit

Table 16.1 Published data on NIMV during PA-H1N1 epidemic

Country of study [first author]	Date published	Patients on NIMV	NIMV failure needing IMV	Reference
Australia [Kaufman, MA]	July 2009	*n* = 4, 66 %	100 %	*MJA* 2009;191:154–156
Spain [Rello, J]	September 2009	*n* = 8, 33 %	75 %	*Critical Care* 2009;13:R148
France [Djibre, M]	October 2009	*n* = 1, case report	None	*Intensive Care Med* 2010;36:373–374
Canada [Kumar, A]	November 2009	*n* = 55, 33 %	85 %	*JAMA* 2009;302:1872–1879
Utah, USA [Miller, RR]	November 2009	*n* = 13, 33 %	85 %	*Chest* 2010;137: 752–758
South African [Koegelenberg, CFN]	March 2010	*n* = 6, 66 %	66 %	*Q J Med* 2010;103:319–325
Portugal [Winck, JC]	March 2010	*n* = 1, case report	None	*Crit Care* 2010;14:408
Brazil [Hajjar, LA]	April 2010	*n* = 8, 50 %	25 %	*Ann Oncol* 2010;21(12):2333–2341
Chilean-Uruguay [Nin, N]	April 2011	*n* = 43, 45 %	77 %	*J Crit Care* 2011;26(2):186–192

- Strict personal protection equipment for health care workers (HCWs)
- Minimal number of individuals caring for the patient
- Strict monitoring of HCWs for signs and symptoms of infection

16.3 NIMV as a Risk for Aerosol Droplet Infection

Recommendations regarding NIMV as a risk for aerosol droplet infection are mainly based on studies published and experiences following the severe acute respiratory syndrome (SARS) epidemic in 2003 (Table 16.1). The pivotal study arguing that NIMV poses high risk of infection spread is based on the assessment of particle dispersion using an experimental model [4]. Smoke was introduced into the lungs of a mannequin while noninvasive ventilation (NIV) was being used. Plumes of smoke emerging from the vented mask were photographed for particle dispersion. So far no study has been conducted to evaluate particle dispersion on humans. Whether a mannequin simulates a live patient using NIMV has been greatly debated, and many argue that the NIMV mask may in fact offer protection from secretions that would have otherwise been dispersed from the infected patient during coughing, sneezing, and speaking. Also, there are no comparative data on particle dispersion between individuals undergoing NIMV and those who do not.

During the SARS outbreak, a study in Hong Kong looked at the efficacy of NIMV in early ARDS patients. It also evaluated the infection risk among HCWs who had direct contact with patients on NIMV [5]. In all, 22 patients (25 %) needed NIMV and 155 HCWs (including doctors, nurses, and health-care assistants)

exposed to patients on NIMV therapy were regularly screened for signs of infection. Coronavirus serology was obtained for 97 % of HCWs. NIMV equipped with expiratory bacterial and viral filters was provided in isolated cubicles in the ward or in the ICU, which were centrally air-conditioned and fitted with exhaust ventilation fans to achieve negative-pressure flow. The study concluded that NIMV was not only effective in preventing IMV in 70 % of patients with acute respiratory failure due to SARS but it effectively reduced the ICU length of stay or avoided ICU admission altogether. Moreover, no infection was noted in any of the 155 HCWs, and their serology tests for coronavirus were negative.

Based on the guidelines from ERS/ESICM, the World Health Organization, the United Kingdom's National Health Services Agency, The Hong Kong Lung Foundation, and the American Association of Respiratory Care, NIMV is currently considered a high-risk procedure during respiratory pandemics. This has led to ICU overuse, strain on available resources, and an increase in IMV-related complications. Further validation of the association between NIMV and infection spread by particle dispersion is needed for planning for future pandemics [2, 6, 7].

Conclusion

Noninvasive mechanical ventilation has a role in the management of early respiratory failure due to PA-H1N1 infection in a strictly controlled environment with close monitoring of HCWs. NIMV has no role in patients with severe respiratory failure and ARDS related to severe PA-H1N1 infection. These patients must be intubated and placed on IMV. However much it is still debated, the potential risk of particle dispersion and spread of infection due to NIMV is present.

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Noninvasive Mechanical Ventilation in Patients with Tuberculosis: Exhaled Breath-Generated Aerosols of *Mycobacterium tuberculosis*

17

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Keywords
Noninvasive mechanical ventilation • Tuberculosis • Aerosols • *Mycobacterium tuberculosis*

17.1 Introduction

Patients with acute exacerbation of tuberculosis can now be treated successfully with noninvasive ventilation (NIV) [1]. NIV is effective not only in cases of rapidly progressive mycobacterial tuberculosis but also in chronic cases where the disease has exacerbated. NIV use may reduce the high demand for intensive care unit (ICU) beds [2]. This is the first study to assess clinically the risk of spread of mycobacterial tuberculosis infection by droplet or aerosol during NIV.

17.2 Infection and Transmission Course of Mycobacterial Tuberculosis

Mycobacterial tuberculosis is spread by infectious droplet nuclei (airborne particles 1–5 μm in diameter) through coughing, sneezing, or vocalization by patients with pulmonary or laryngeal tuberculosis [3]. Mycobacterial tuberculosis invariably spreads through air rather than by direct contact. In other words, a susceptible individual inhales droplet nuclei containing *Mycobacterium tuberculosis*, following which infection is established when droplet nuclei reach the pulmonary alveoli

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through the upper respiratory tract. Spread of the infection in the body then occurs, first by lymphatic and then by hematogenous dissemination. The immune response appears within 2–12 weeks of the initial infection, when the immunological test becomes positive [3].

There are no restrictions on tuberculosis patients coughing, sneezing, or talking during NIV management. Thus, the formation of airborne infectious droplet nuclei is expected.

17.3 Does Aerosol Diffusion Occur in NIV?

According to Simonds, NIV is a droplet-generating procedure rather than an aerosol-generating procedure, producing droplets of >10 μm. Because of their large mass, most droplets cascade down onto nearby surfaces within an area of 1 m^2. The only device used clinically to produce aerosols is the nebulizer, and its output profile is consistent with nebulizer characteristics rather than the dissemination of large droplets [4]. These findings suggest that health care workers (HCWs) providing NIV and working within 1 m^2 of an infected patient should be provided a higher level of respiratory protection. Infection control measures designed to limit aerosol spread may have less relevance for this procedure.

According to the findings of studies aimed at determining clinical evidence of the risk of transmission of acute respiratory infections to HCWs caring for patients undergoing aerosol-generating procedures, some procedures that are potentially capable of generating aerosols are associated with increased risk of acute respiratory infection transmission. They represent a risk factor for transmission. The most consistent association across multiple studies was identified to be tracheal intubation [5]. If tracheal intubation carries a greater risk of transmission of *M. tuberculosis*, the choice of NIV over tracheal intubation may be warranted when artificial respiration management is required for the tuberculosis patient in acute respiratory failure (ARF).

According to Dharmadhikari, the use of surgical face masks in patients with multi-drug-resistant tuberculosis significantly reduced transmission, offering an additional measure for reducing transmission from infected patients [6]. On the other hand, when tuberculosis patients were not wearing a mask, 28 % were found to produce cough aerosols capable of being cultured [7]. If we surmise that the mask used in NIV plays the role of a surgical mask, providing NIV to infected patients may be useful in reducing tuberculosis transmission.

Judging from the above reports, it can be argued that NIV in tuberculosis has a curative effect and helps prevent or reduce the transmission of bacteria from patient to HCW. The HCWs providing NIV and working within 1 m^2 of an infected patient are at high risk of infection and should be provided a higher level of respiratory protection. Although tracheal intubation involves a closed-circuit system that appears to reduce the risk of tuberculosis transmission, the risk is in fact increased because of the increased level of contact between HCWs and patients.

17.4 Infection Control Measures with Regard to NIV in Tuberculosis Patients

The private sickroom for patient isolation, used for tuberculosis patients among others, is called the air infection isolation room. Table 17.1 summarizes the main criteria involved in the utilization of this room according to the Centers for Disease Control and Prevention guidelines [8]. Wearing an N95 mask is recommended as it filters >95 % of particles >0.3 μm in diameter and meets the performance standards of the National Institute for Occupational Safety and Health.

Because it has been reported that tuberculosis spreads through inadequate sterilization of bronchoscopy apparatus rather than by expectoration and droplet nuclei from respiratory equipment, semi-critical respiratory equipment requires a high level of sterilization to eliminate *M. tuberculosis* [9]. This is natural, according to the definition of high-level sterilization. Because in some cases the sterilization equipment is not sufficiently effective to destroy *M. tuberculosis*, attention to this problem is required. In addition, special attention is necessary because various aerosol-producing procedures may cause medically related tuberculosis transmission (Table 17.2) [8].

Tuberculosis transmission through noncritical appliances or from environmental surfaces has not yet been reported. Therefore, even when appliances used in tuberculosis patients are not anticipated to be contaminated from expectoration, they

Table 17.1 Summary of key criteria for the air infection isolation room

1. Set to negative pressure compared with the neighboring areas
2. Ventilation at >12 times/h (new construction, repair facilities) or six times per hour (existing facilities) can be accomplished. It is set up under appropriate open air or set room air so it goes through super-high-efficiency filtration before it circulates to other areas.
3. Bathrooms and restrooms are established.
4. Keep the door of the room closed.
5. All healthcare workers entering the room wear an N95 mask.

Table 17.2 Aerosol-producing procedures that may cause medically related tuberculosis transmission

Bronchoscopy, laryngoscopy
Tracheal intubation
Transtracheal aspiration
Expectoration-induced measures
Nebulizer causing a cough
Other respiratory measures
Intragastric aspiration, insertion of a nasogastric tube
Washing a patent tuberculosis abscess
Homogenization and lyophilization of organisms
Autopsy an deceased untreated tuberculosis patient
Handling a composition that may include tuberculosis
Clinical inspection of tuberculosis

Table 17.3 Disinfectants used for *Mycobacterium tuberculosis*

Semi-critical appliance (including a bronchus endoscope)
2.0–3.5 % Glutaral (>20 min after previous washing)
0.55 % Phthalal (12 min)
0.3 % Peracetic acid (exposure time is temperature-dependent)
Noncritical surface (sterilization is especially necessary)
Heated water (at 80 °C for 10 min)
Alcohol
0.5–1.0 % Cresol soap liquid
0.2–0.5 % Alkyl diaminoethyl glycine hydrochloride (liquid)
Sodium hypochlorite (liquid) of >1,000 ppm (invalid with low concentrations)

Table 17.4 NIV in acute exacerbations of pulmonary tuberculosis sequelae

Country [author], ref	Study design, *n*	Type ARF–TB	Interface (mask)	NIV failure	Adverse effects to HCW[a]	Home mechanical ventilation after AEPTS
Japan, [Tsuboi T], [11]	Cohort, prospective (17)	AEPTS in mixed group	Nasal	0	No	Yes
Japan, [Machida K], [12]	Retrospective survey (58)	AEPTS	Nasal	0	No	Yes
Spain, [Prats Soro E], [13]	Case report (1)	AEPTS	Nasal	0	No	Yes
Germany, [Schulz MR], [14]	Cohort, prospective (26)	AEPTS	Nasal	0	No	Yes
India, [Agarwal R], [15]	Cohort, case series (3)	ARDS, MyTB, AEPTS	Face	0	No	No
Japan, [Tsuboi T], [11]	Cohort, retrospective (50, 66)	AEPTS	Face	8.0 %	No	No
Japan, [Utsugi M],[16]	Case report (1)	ARF, miliary TB, AEPTS	Face	0	No	No
Japan, [Aso H], [2]	Cohort, prospective (58)	AEPTS	Face	13.8 %	No	1.7 %

AEPTS acute exacerbations of pulmonary tuberculosis sequelae, *ARF* acute respiratory failure, *CRF* chronic respiratory failure, *HCW* health care workers, *MyTB Mycobacterium tuberculosis*, *NIV* noninvasive ventilation, *TB* tuberculosis
[a]Complications: transmission of MyTB among HCWs

should be washed, wiped, and sterilized as usual, which is deemed adequate for the sickroom [10].

Sterilization for *Mycobacterium tuberculosis* requires the use of one of the disinfectants listed in Table 17.3. Benzalkonium chloride and chlorhexidine gluconate, which are both low-strength disinfectants, are ineffective.

The major clinical studies regarding the use of NIV during acute exacerbations of pulmonary tuberculosis are summarized in Table 17.4.

Key Major Recommendations

- It can be argued that NIV in patients with tuberculosis has a curative effect and helps prevent or reduce the transmission of bacteria from the patient to HCWs.
- The HCWs providing NIV and working within 1 m^2 of an infected patient are at a high risk of infection and should be provided a higher level of respiratory protection.
- Noninvasive ventilation in tuberculosis patients needs specific infection control measures.
- Special attention is necessary because various aerosol-producing procedures may cause medically related tuberculosis transmission.

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Noninvasive Mechanical Ventilation After Chemical Disasters

18

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Noninvasive mechanical ventilation • Chemical agent • Disasters

18.1 Introduction

The term *chemical agent* has traditionally been defined as a substance intended for use in military operations to kill, seriously injure, or incapacitate humans (or animals) through its toxicological effects [1]. These agents have been used in warfare for thousands of years. Recent events, such as the 1994 sarin nerve agent attack in Matsumoto, Japan and the 1995 Tokyo subway destructive release of this chemical, have made it clear that health care providers need to be prepared to handle chemical agent attacks.

According to numerous government agencies and the military, at least ten countries have the capability to produce and disseminate chemical and biological weapons. These statistics do not include the unknown (or unpublished) innumerable terrorist organizations that can effectively manufacture and strategically deploy such agents. Therefore, it is obvious that a threat exists [2].

Although most of these weapons have the potential for mass casualty application, quite often they are used covertly with small-dose exposures that may lead to

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a delayed or subtle presentation. Consequently, it is vital for health care providers to be vigilant and trained to recognize signs and symptoms of a chemical agent exposure so as to report and treat each case appropriately.

This chapter focuses on the five most common types of chemical warfare agents used, their clinical presentations, and medical management after decontamination including the possible application of noninvasive ventilation.

18.2 Analysis of Main Topics and Discussion

Chemical warfare agents can be categorized by their physiological action or practical application. Based on this schema, five classes exist: nerve agents, vesicants, cyanides, pulmonary agents, riot-control agents. Each group has a different pathophysiological presentation that is important to understand in order to apply appropriate treatment.

18.2.1 Nerve Agents

Nerve agents comprise a group of organophosphates that were developed during the 1930s as a method of chemical warfare. Today, exposure to nerve agents would most likely come from a terrorist attack or a leak from military storage. The principal nerve agents are sarin, tabun, soman, cyclosarin, and methylphosphonothioic acid. As the name indicates, their primarily affect is on the nervous system by binding to and inhibiting normal functioning of the enzyme acetylcholinesterase. Normally, this enzyme acts to break down acetylcholine (ACh) in the cholinergic system. ACh is a neurotransmitter that activates and controls muscular contraction. It also participates in the diffuse modulatory system, where it causes antiexcitatory actions. Because nerve agents inhibit the means by which ACh is eliminated, excess ACh accumulates, leading to nerve impulses being continually transmitted and to prolonged stimulation of the affected tissues [3].

The acuity and severity of symptoms caused by a nerve agent highly depend on its route and site of entry into the body. Most often, nerve agents enter the body either through inhalation or direct contact at the skin or eyes. Particularly, the poisonous effect is quickest, within seconds to minutes [4–6], when the agent (vaporized or aerosolized) is absorbed via the respiratory system. Owing to the myriad blood vessels in the lung, the inhaled nerve agent rapidly diffuses into the pulmonary circulation and thus reaches the target organs [4–6]. Oral and transdermal absorption generally do not present clinically until 3 and 12 h, respectfully, after contact [4–6].

After the nerve agent has entered the body, detrimental symptoms and effects begin to rapidly appear. Initial symptoms are usually a runny nose, sweating, drooling, and tightness in the chest. Afterward, the nerve agent progressively causes difficulty breathing and renders many bodily functions inept. The victim begins to salivate, urinate, lacrimate, defecate, and vomit involuntarily. In other words, the

victim starts to lose control of many parts of his or her body. Miosis and rhinorrhea result from contact with the eyes and nose, respectively. The nerve agent then continues to damage many of the victim's bodily functions, causing increased motility and an increase in the level of secretion of the gastrointestinal tract. Nausea, vomiting, and diarrhea usually follow. The nerve agent may also initially cause muscular fasciculations and weakness, with gradual development into muscular flaccidity. Aside from the skeletal effects, the nerve agent also produces cardiovascular symptoms. Elevation of the heart rate is multifactorial including hypoxia and fright, but it may also be due to decreased vagus nerve activity. Bradyarrhythmias often occur. After a high enough exposure, the victim can also suffer from disruption of normal central nervous system functions, leading to apnea, seizures, or loss of consciousness. The array of symptoms is often summarized in the mnemonic DUMBELS (diaphoresis/diarrhea, urination, miosis, bronchorrhea/bronchospasm, emesis, lacrimation, salivation) [6].

Several treatments are available that can curtail the effects of nerve agents. Atropine and pralidozime (2-PAM) chloride, each of which is administered intramuscularly, are primarily used to reverse the effects of nerve agents. Atropine is an anticholinergic drug that acts as a competitive antagonist at muscarinic receptors. Atropine counters/resists the actions of the vagus nerve, blocks ACh receptor sites, and decreases bronchial secretions. Because it functions as a competitive antagonist of muscarinic ACh receptors, and ACh is the primary neurotransmitter utilized by the parasympathetic nervous system, atropine decreases the parasympathetic activity of all muscles and glands regulated by the parasympathetic nervous system [6]. Generally, atropine is used to decrease bronchial secretions. 2-PAM chloride is used to reverse the binding of the nerve agent, regenerate the previously poisoned enzyme acetylcholinesterase, and enable the enzyme to metabolize ACh. 2-PAM chloride works best on nicotinic receptors.

Aside from atropine and 2-PAM chloride, homatropine and benzodiazepine are also used. Homatropine is an anticholinergic medication that functions to treat miosis. Homatropine inhibits the parasympathetic nervous system by inhibiting muscarinic acetylcholine receptors. Benzodiazepine (anticonvulsant) is used to treat seizures that a nerve agent victim may experience.

It is important to note that respiratory failure is the principal cause of death in nerve agent exposure [5, 7]. Rapid progression of respiratory failure due to nerve agent exposure is twofold. (1) Accumulation of ACh in the respiratory organs causes overstimulation of the parasympathetic pathway, resulting in excess secretions, toxic pulmonary edema, and severe bronchoconstriction. (2) Respiratory muscular paralysis, particularly of the diaphragm, and central depression of the respiratory centers further contribute to eventual respiratory arrest. Death caused by nerve agents is commonly compared to death by suffocation. Therefore, alongside the aforementioned antidotes, airway management is crucial for treatment.

Current therapeutic protocols stress the need for urgent laryngoscopy and intubation, with concomitant provision of positive-pressure ventilation until signs of muscle paralysis disappear [7]. This is difficult to accomplish in the setting of mass casualties because of the shortage of trained professionals. Also, the equipment is

cumbersome. Conventional face/nasal mask noninvasive positive-pressure ventilation is contraindicated in the setting because of the excessive pulmonary secretions and neuromuscular dysfunction. Therefore, it is unlikely it would be beneficial in a victim of exposure to a nerve agent. A relatively new refined resurrection of the negative-pressure ventilator (often referred to as the "iron lung") may provide a solution.

An external high-frequency oscillation (EHFO) ventilator, the MRTX respirator (United Hayek Medical, London, UK), has been shown to be efficacious in providing proper, noninvasive artificial ventilation to normal and sick lungs. The power unit works by creating cyclic pressure changes inside the cuirass (a clear, flexible plastic enclosure surrounding the chest and abdomen with soft foam rubber borders to create an airtight seal around the patient). The negative pressure creates chest expansion and thus inhalation. The positive pressure creates chest compression and thus exhalation. Thus, both inspiratory and expiratory phases are actively controlled, and the chest is oscillated around a variable negative baseline pressure [7]. In addition to providing respiratory support, EHFO potentially preserves cardiac output, compared with conventional positive-pressure ventilation, and actively aids in secretion expectoration through forceful clearance. These qualities manage the direct negative cardiovascular and respiratory effects induced by nerve agents. The unit is lightweight, easy to operate, portable, and requires minimal training. Although EHFO appears to be a superb ventilator support system in the setting of nerve agent exposure, the lack of adequate separation of the digestive from the respiratory tracts makes endotracheal tube placement a prudent measure [7].

18.2.2 Vesicants

Vesicants are alkylating agents that affect cellular division and DNA synthesis by binding a number of molecules via a reactive sulfonium ion with greatest affinity for nucleic acid and sulfur and sulfhydryl groups on proteins. Mustard gas (or sulfur mustard) is one of the most notable vesicants. It was first used as a weapon during World War I and more recently in the Iran–Iraq conflict during the 1980s. Other agents include lewisite, nitrogen mustard, and phosgene oxime.

As with most chemical agents, effects of vesicants are based on the site of contact, time of exposure, and concentration of the agent, whereas the severity and latency of the onset are influenced by the environment. Vesicants are known for their delayed manifestations. The hallmark of dermal exposure to mustard is a prolonged asymptomatic period [1]. This latency period is shortened in the presence of high environmental or body temperature and moist skin.

These agents are highly lipophilic and easily penetrate mucosal surfaces. The main characteristic of vesicants is their direct toxicity to organic tissue, inducing chemical burns and blisters on both external and internal body surface areas including skin, eyes, mucous membranes, and lungs. Respiratory symptoms usually present 4–6 h after exposure, initially involving the upper respiratory tract and then progressing lower. Patients often complain of sinus pain, irritation of the nose, sore throat, and a hacking cough followed by hoarseness and loss of voice. Laryngeal

spasms may occur. Large-dose inhalations affect the lower airway, causing shortness of breath and a productive cough. This may be due to the development of a patchy pneumonia, purulent bronchitis, or even hemorrhagic bronchitis. Pseudomembranes can arise as a result of mucosal necrosis. They can be complicated by obstruction in the bronchi or trachea leading to asphyxiation, the most common cause of death [1, 8, 9]. Survivors are often plagued by chronic conditions involving the eyes, skin, and lungs, including corneal thinning and opacification, severe eczema, skin cancers, chronic bronchitis, and pulmonary fibrosis [8, 9].

There is not antidote for sulfur mustard exposure, and treatment after decontamination is largely supportive. Mild respiratory tract injuries often resolve without intervention. Bronchodilators may be useful for spasms, antibiotics for pneumonia, and bougienage for pseudomembranes. Although infection is the most important complication of healing mucosal damage, prophylactic antibiotics are not recommended. More severe cases may require management on the burn unit. Airway stabilization should be accomplished through conventional means [1–9].

18.2.3 Cyanide

Cyanide is a chemical blood agent that was first used during World War I. The Germans most infamously used it during the Holocaust, and the United States used it to execute prisoners in the gas chamber from 1924 to 1999. Cyanide is colorless, and some have described it as having an almond-like odor. As a chemical weapon, cyanide exists as hydrogen cyanide and cyanogen chloride. Cyanide can also exist in all three states of matter. As a solid (cyanide salts), cyanide can be absorbed through the skin and eyes or through ingestion. As a liquid or gas, cyanide is most perilous because it can enter the body through inhalation. Cyanide can enter and spread in water, soil, or air through natural and industrial means. It exists as gaseous hydrogen cyanide in air.

Cyanide can affect its victim extremely quickly; how quickly often depends on the condition by which cyanide is being released or absorbed. For example, if the victim inhales cyanide in a closely enclosed area, it can cause death within 10 min. Cyanide's effects are typically curtailed when it is released into a spacious/open area, where it can diffuse and evaporate into a large number of locations. Although ingesting cyanide can be detrimental, inhaling the gas presents the most harm as respiratory failure is the major cause of death in cyanide exposure. Cyanide is taken up by blood and lymphatics and is then distributed systematically. As cyanide is circulated throughout the body, various cells absorb it. Entering the cells' mitochondria, cyanide displaces oxygen bonded to protein [10, 11]. Proteins that are rendered inept by the actions of cyanide are called cytochrome [4]. Cyanide acts as a mitochondrial cytochrome oxidase inhibitor. These inhibitors form stable complexes with ferric iron, thereby inhibiting cellular respiration. Cellular respiration ceases because the final step in electron transfer between the substrate hydrogen and oxygen in the mitochondria is blocked (essentially poisoning mitochondrial electron transport chain within cells), thus effectively preventing or hindering the cells' ability to use oxygen absorbed from the bloodstream. Without that energy

production, the cells throughout the body die, resulting in death [10]. Even if the victim is able to recover, he or she often continues to suffer from heart and brain complications because they require the most oxygen.

The acuteness and severity of the clinical condition after cyanide exposure depends on the amount of cyanide to which the victim is exposed. A person exposed to a small amount of cyanide through inhalation, absorption through the skin, or ingestion is likely to show symptoms within minutes of exposure: rapid breathing, restlessness, dizziness, weakness, headache, nausea, vomiting, rapid heart rate. If there is a lengthy exposure to a large dosage of cyanide, other effects maybe exhibited, including convulsions, hypotension/shock, pulmonary edema, bradycardia followed by tachycardia, syncope, lung injury, and respiratory failure, which would result in death within 8–10 min. Also, being toxic itself, the chlorine in cyanogen chloride can cause eye and respiratory tract irritation and, potentially, delayed pulmonary toxicity [11].

There are various ways to restrain the effects of cyanide or to remove traces of cyanide. Any traces or source of cyanide on the victim should be removed by thoroughly washing the region(s) with soap and water. The primary treatment process includes first using a small inhaled dose of amyl nitrite. Sodium thiosulfate is then applied intravenously. The sodium nitrate oxidizes the hemoglobin's iron from the ferrous state to the ferric state, thereby converting hemoglobin into methemoglobin. Cyanide has a high binding affinity for methemoglobin; as a result, instead of binding to cytochrome oxidase, cyanide binds to methemoglobin, and the methemoglobin is converted to cyanmethemoglobin. Lastly, sodium thiosulfate is applied intravenously to convert cyanmethemoglobin to thiocyanate, sulfite, and hemoglobin. The thiocyanate is excreted in the urine. Sodium thiosulfate also provides a source of sulfur that the enzyme rhodanese—the major pathway for metabolism of cyanide—utilizes to detoxify cyanide [11]. Like methemoglobin, cyanide has a high binding affinity for cobalt. Hydroxocobalamin, which contains cobalt, becomes cyanocobalamin (eliminated through urine) after binding to cyanide [11]. Thus, cyanide binds to hydroxocobalamin instead of cytochrome oxidase. Both procedures are used to reverse cyanide binding to cytochrome [4]. Another form of treatment for cyanide poisoning is to provide the victim with oxygen and assisted ventilation. This is because the human liver has the ability to metabolize cyanide (particularly low doses of it). If the victim is kept stable with oxygen and assisted ventilation, the liver can gradually eliminate the cyanide.

18.2.4 Pulmonary Agents

The first major usage of pulmonary agents dates back to World War I. Germany utilized phosgene as a chemical warfare agent at Verdun in 1917. Pulmonary agents, also called choking agents, are chemical weapons that preclude the victim from breathing normally. The primary pulmonary agents include chlorine, phosgene, diphosgene, and chloropicrin—with phosgene being the most commonly used and most dangerous. Under regular conditions, phosgene is a colorless gas that smells like sweet, newly mown hay.

Pulmonary agents, specifically phosgene, can cause pulmonary edema. Its effects are most perilous when it is inhaled. The precise mechanism by which pulmonary agents work remains somewhat of a conundrum, but it is known that it affects the permeability in the blood–air barrier. Once phosgene is dissolved, it hydrolyzes to form carbon dioxide and hydrochloric acid. Release of hydrochloric acid during phosgene hydrolysis causes the early ocular, nasal, and central airway irritation. The carbonyl group readily participates in acylation reactions with amino, hydroxyl, or sulfhydryl groups—reactions that account for the major pathophysiological effects of phosgene [12–14]. Acylation occurs at the alveolar–capillary membrane and leads to leakage of fluid from those capillaries into the interstitial alveolar space [12–14]. Initially, lymphatic drainage from the parenchyma resists this leakage into the pulmonary interstitium, but eventually the lymphatic drainage becomes inept against the effects of phosgene. Following a latent period, fluid eventually reaches alveoli and peripheral airways, leading to increasingly severe dyspnea and clinically evident pulmonary edema [12–14].

The signs and symptoms after exposure to pulmonary agents usually start to appear shortly after contact. Symptoms are seen within 12 h and can cause death within 24–48 h. After a clinical latent period, the duration of which varies depending on the intensity of exposure, ranges from 20 min to 24 h. Phosgene produces mucosal irritation and pulmonary edema that leads to death. After the latent period, the victim typically shows mucous membrane irritation, seemingly because of the hydrochloric acid produced from hydrolysis of phosgene. Alongside the mucous membrane irritation, the victim suffers from evanescent burning sensation in the eyes with lacrimation, blurred vision, burning in the throat, laryngeal spasm, coughing, headache, chest pain, tightness in the chest, and coughing. The most prominent symptom following the clinical latent period is dyspnea. These sensations reflect hypoxemia, increased ventilatory drive, and decreased lung compliance as a consequence of accumulation of fluid in the pulmonary interstititum and peripheral airways [12, 13]. Cyanosis become visible if a large amount of hemoglobin is deoxygenated. Furthermore, the sequestration of plasma-derived fluid in the lungs may lead to hypovolemia and hypotension, influencing oxygen delivery to the brain, kidneys, and other crucial organs [12–14]. Normally, hypoxemia, hypovolemia, respiratory failure, or a combination of the three contributes to death.

There are several treatment options for someone exposed to a pulmonary agent. First and foremost, one should terminate the exposure, which can be done by either quarantining the victim from surrounding contamination or by removing the victim from the contaminated environment. The ABCs of resuscitation should be performed as needed because it is highly important that a stable, clear airway is established in the victim. The victim's circulatory condition should be vigilantly monitored because there is the risk of hypotension provoked by pulmonary edema. The victim's physical activity must be limited also as the slightest physical activity may reduce the clinical latent period and intensify the severity of respiratory signs and symptoms. There are several ways to prevent or treat specific effects of pulmonary agent exposure. To prevent and/or treat bronchospasm, one should prepare to manage airway secretions. After exposure to phosgene, the airways are covered by

moist secretions and can be treated by suctioning and drainage. Bronchospasm can also occur in victims who have reactive airways, and they should be treated with bronchodilators. Systemic steroid therapy is also indicated for treatment of bronchospasm [12–14]. To prevent/treat pulmonary edema, positive airway pressure is useful. Also, early use of a positive-pressure mask can be helpful for monitoring the effects of pulmonary edema. Oxygen therapy is mandatory to prevent/treat hypoxia, and it might require supplemental positive airway pressure [12–14]. Intubation with ventilatory support may also be needed. To prevent/treat hypotension, which is aggravated by positive airway pressure, immediate intravenous administration of either crystalloid or colloid may need to be supplemented by judicious application of a pneumatic anti-shock garment [12–14].

18.2.5 Riot Control Agents

Riot control agents are often used as a mean of law enforcement with the intention of controlling or adjourning a public disturbance. They are also used for personal protection (e.g., pepper spray). Riot control agents exist as chemical compounds that cause irritation to the eyes, mouth, throat, lungs, and skin, consequently rendering the victim temporarily incapable of functioning normally. Victims usually are forced to close their eyes and hold their breath—resulting in their becoming incapacitated. The most common riot control agents are chloroacetophenone (CN), chlorobenzylidenemalononitrile (CS), chloropicrin (PS), bromobenzylcyanide (CA), and dibenzoxazepine (CR). Riot control agents exist as solids with low vapor pressure. They therefore can be released into the air as fine particles or in solution. The primary dispersion methods include spray cans, spray tanks, or grenades. Once released in the air, the victim can be exposed to it via skin contact, eye contact, or inhalation.

Once exposed to the riot control agent, the victim usually starts showing signs of irritation within seconds. The extent of poisoning caused by riot control agents depends on the amount of riot control agent to which a person was exposed, the location of exposure (indoors versus outdoors), how the person was exposed, and the duration of the exposure [12, 15–17]. Understandably, the riot control agent is most detrimental when it is dispersed indoors (less space to spread), and the victim is exposed to it for a prolonged time. The exact mechanism of riot control agents is not well known, but fortunately the mechanism does not have to be completely known to treat the poisoning. What is known is that the riot control agents act on the eyes and mucosal membranes, causing intense pain and lacrimation to temporarily incapacitate the victims. If a high concentration is disseminated, the riot control agent causes respiratory tract irritation. The main targets of the riot control agent are sulfhydryl-containing enzymes. Inactivation of these enzyme systems is often associated with causing tissue injury.

The signs and symptoms after exposure usually last 15–30 min but can last much longer if exposure has been prolonged. The main effects of riot control agents are pain, burning, and irritation of exposed mucous membranes and skin [12, 15–17]. The eye is most affected by riot control agents. Once in contact with the eyes, the riot control agents cause a sensation of conjunctival and corneal burning and lead to

tearing, blepharospasm, and conjunctival injection. Blepharospasm causes the lids to close tightly and produces transient blindness, an effect that could inhibit the recipient's ability to fight or resist [12, 15–17]. The riot control agent has similar effects on the nose and mouth. By coming into contact with the mucous membranes of the nose, the agent causes a burning sensation, rhinorrhea, sneezing, and increased salivation. It also causes a tingling and burning sensation if it comes into contact with the skin, sometimes leading to erythema and hypersensitivity of the skin. Once inhaled, the riot controls agent triggers burning and irritation of the airways with bronchorrhea, coughing, and perception of a tight chest or an inability to breathe [12, 15–17]. There is no evidence that riot control agents cause permanent lung damage. Although they do not specifically disturb the gastrointestinal tract, riot control agents can cause retching or vomiting if there was a high concentration of the agent. The affects on the cardiovascular system are more definitive. In almost all victims, either prior to or immediately after exposure there is a temporary elevation in heart rate and blood pressure. It is believed that this increase is not due directly to the riot control agents but is, instead, caused by angst or the initial pain.

The effects of riot control agents are temporary and usually begin to wane after 15 min—once the victim exits the area of contamination to fresh, clean air. The victim should also quickly remove his or her contaminated clothing to accelerate the recovery process. However, if the victim is exposed to a high concentration or a prolonged duration of the riot control agent, there is a possibility that he or she may suffer further deterioration. Death after being exposed to a prolonged duration of riot control agent is due to severe airway damage. Most victims, though, do not suffer death and do not require medical treatment because the effects of riot control agents are self-limiting and fade within 15–30 min. Some victims, however, seek treatment for eye, airway, or skin irritation. The eye should be vigilantly flushed with water. Topical solutions or antibiotics can be used to alleviate the irritation. Treatment for airway irritation may become more complicated. Asthmatic victims can suffer from bronchospasm and mild distress hours after exposure. Victims with chronic bronchitis or emphysema can experience more severe respiratory distress. Management includes oxygen administration with assisted ventilation if necessary, bronchodilators if bronchospasm is present, and specific antibiotics dictated by the results of sputum studies [2]. Treatment of the skin can become complicated. If erythema persists more than 1–2 h, it may require the use of soothing compounds such as calamine, camphor, and mentholated creams. Small vesicles should be left intact, but larger ones ultimately break and should be drained. Irrigation of denuded areas several times a day should be followed by application of a topical antibiotic [12, 15–17].

18.3 Role of Noninvasive Mechanical Ventilation

The main cause of death as a result of exposure to a chemical agent is respiratory failure. The injury could result from excessive pulmonary secretions and respiratory muscle paralysis due to nerve agent exposure; patchy pneumonia with purulent or hemorrhagic bronchitis and laryngospasm due to exposure to vesicants; pulmonary edema and severe hypoxemia associated with cyanide exposure; or bronchial

mucosa irritation, excessive secretions, and pulmonary edema after pulmonary agents and riot control gas. Mechanical ventilation is essential for stabilizing the airways and maintaining adequate oxygenation. The data on noninvasive positive-pressure ventilation (NPPV) are unclear as most of the patients are hemodynamically unstable with possible injury to the airways. NPPV might have a role in avoiding reintubation after successful intubation or might be used as a bridge from intubation to decrease the ventilatory days and risk of nosocomial pneumonia. NPPV can be used with caution in monitored settings in casualties with mild respiratory injury from vesicants or mild hypoxemia related to cyanide exposure during antidote therapy. NPPV is indicated in the treatment of noncardiogenic pulmonary edema. It can be used, with caution, in patients with pulmonary edema secondary to exposure to a pulmonary agent. NPPV is applied with caution in critical care settings in hemodynamically stable patients with a readiness to intubate the patient if the condition deteriorates.

Conclusion

Pulmonary failure is the main cause of death after exposure to chemical agents. Mechanical ventilation is essential in the supportive care of the casualties [18]. Stabilizing the airways and maintaining adequate gas exchange is the goal of mechanical ventilation. The role of NPPV is unclear. It can be used with caution in ICUs. Patients should be selected properly. Hemodynamic stability is essential. NPPV can be applied in mild cases and within the latent period after exposure along with antidote therapy. Adjuvant therapy includes fluid resuscitation, intravenous steroids, bronchodilators, and antibiotics if indicated.

Major Key Recommendations

- The clinical distinction between exposures to chemical agents may not always be apparent upon initial presentation. Therefore, the focus of each case should be on airway stability and the potential for future compromise.
- Decontamination, antidote, and supportive care are the main therapeutic elements.
- The role of noninvasive mechanical ventilation is unclear at this time. It should be used with caution in ICU settings with a readiness to intubate.

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Inhalational Anthrax and Bioterrorism: Key Recommendations for Acute Respiratory Failure

19

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Keywords
Anthrax • Bioterrorism, acute respiratory failure

19.1 Introduction

Anthrax is caused by exposure to *Bacillus anthracis* an aerobic, Gram-positive, spore-forming bacterial infection that most commonly infects herbivore mammals. Human infection occurs in those with close exposure to infected animal products. In fact, the first reported cases of anthrax, during the mid-1800s, were related to the textile and tanning industries in both England and Germany [1]. Infections were first documented in mill workers who were frequently exposed to imported animal fibers contaminated with *B. anthracis* spores.

Anthrax occurs mainly in three forms: cutaneous, gastrointestinal, inhalational. The bacillus spores enter a body cavity either through skin contact, ingestion, or inhalation. Cutaneous anthrax, contracted by human contact with infected animals or their by-products, accounts for approximately 95 % of anthrax cases [2]. The cutaneous form of the disease is easily treatable and has a good prognosis. Gastrointestinal anthrax is caused by ingestion of poorly cooked meat. It is rare, with only one documented case in the United states during the past century [3, 4]. Although rare, pulmonary anthrax can also be contracted by inhalation of the microorganism. This form carries a worse prognosis and thus is a greater challenge to physicians.

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Table 19.1 Clinical presentation of inhalational anthrax

Prodromal stage
Fever
Dry cough
Myalgias
Malaise
Occasional chest pain
Fulminant
Sudden rising fevers
Dyspnea
Cyanosis
Diaphoresis
Hemoptysis
Stridor
Hemorrhagic pneumonitis

This once antiquated pathogen has in recently attracted great interest in the modern world because of its potential role as a biological warfare agent. Bioterrorism represents the greatest risk for an epidemic outbreak, which was best illustrated by the accidental release of "weapons-grade" anthrax in Sverdlovsk, Russia in 1979 and most recently in the United States, with nine reported cases [5, 6]. The mortality rate associated with this disease has improved greatly over the past century. In cases reported before 1976 the mortality rate was 94 % in naturally occurring cases, 86 % in Sverdlovsk, and 46 % in the U.S. outbreak [7, 8]. This improvement in overall survival can be accredited to earlier diagnosis, multiple-antibiotic therapy, and improved ventilatory interventions.

19.2 Analysis

Inhalational anthrax occurs when aerosolized spores (2–3 μg) are inhaled and reach the lower respiratory tract up to the alveoli. Once in the respiratory tract, alveolar macrophages phagocytose and carry spores to local mediastinal lymph nodes, where they germinate and produce bacterial toxins that eventually lead to a hemorrhagic mediastinitis [9]. The vegetative bacilli are released from infected macrophages, multiply in the lymphatic system, and then enter the bloodstream and secrete toxins, leading to fulminant septicemia.

The exotoxins produced are composed of three proteins: protective antigen (PA), lethal factor (LF), edema factor (EF). LF and EF alone are not toxic, but in combination with PA they form two toxins. PA plus LF form the lethal toxin, and PA plus EF form the toxin that causes edema. The PA component helps carry the proteins across cell membranes and releases LF into the cytoplasm of the cells. The potential actions of these two toxins have been implicated in septic shock in patients, but the exact mechanism is not well understood.

The clinical presentation of inhalational anthrax has been well described in case studies (Table 19.1). It is a disease with a biphasic course. At the outset it presents with

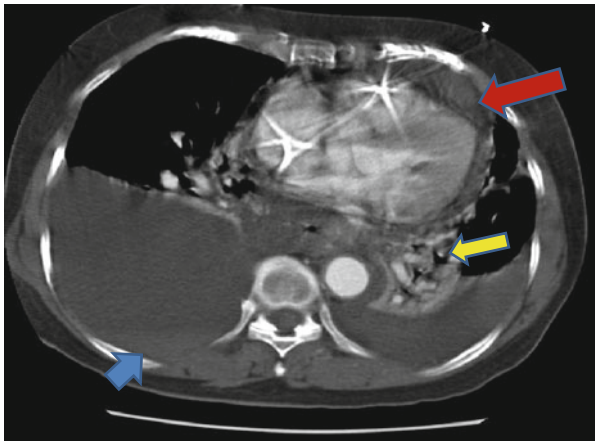

Fig. 19.1 CT with contrast of patient with inhalational anthrax. Important aspects are; bilateral effusions, with erythrocyte sediment seen the left lung base (*blue arrow*) indicative of hemorrhagic pneumonitis, collapsed left lung (*yellow arrow*), as well as a pericardial effusion (*red arrow*)

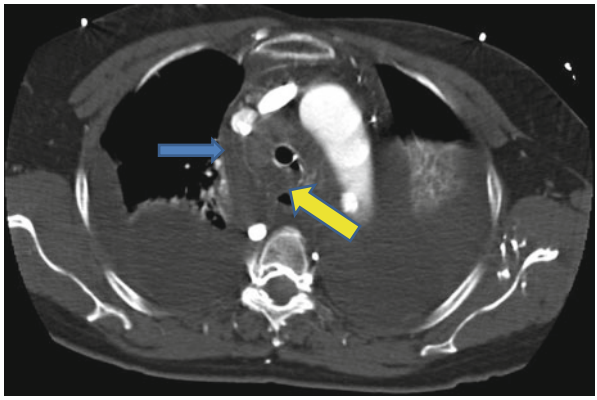

Fig. 19.2 CT with contrast of patient with inhalational anthrax. Important aspects are illustrated here are the widened mediastinum (*blue arrow*) and extensive lymphadenopathy (*yellow arrow*)

flu-like symptoms that can progress from hours to days and then briefly resolve. This stage is manifested by fever, dry cough, myalgias, malaise, and occasional chest pain. Few physical findings are noted at this time. This initial stage is followed by a fulminating stage that presents with sudden rising fever, dyspnea, cyanosis, diaphoresis, hypoxemia, hemoptysis, and stridor [10]. This condition progresses to septic shock, respiratory failure leading multiple organ failure, and eventually death in as short an interval as 24 h.

Patients with progressive inhalational anthrax are typically found to have mediastinal adenopathy and hemorrhagic pleural effusions that can be detected on chest radiography [11] (Figs. 19.1 and 19.2). Pathology examination usually shows a focus of necrotizing hemorrhagic pneumonitis at the portal of infection as well as hemorrhage and necrosis of the peribronchial and mediastinal lymph nodes.

The Centers for Disease Control and Prevention (CDC) set the criteria for anthrax definition in 2001. The initial diagnosis of anthrax is usually made by Gram staining of blood, cerebrospinal fluid, pleural fluid, or a skin lesion, in addition to a compatible clinical picture. The presence of Gram-positive bacilli or rods is highly suspicious for anthrax. The polymerase chain reaction may help in the early diagnosis of

the disease along with an enzyme-linked immunosorbent assay test, time-resolved fluorescence test, immunochromatography (RedLine Alert), fluorescence resonance energy transfer assay, europium nanoparticle-based immunoassay, and electrophoretic immunotransblot reaction.

The mainstay of anthrax treatment is early antibiotic therapy. The CDC recommends treatment with intravenous ciprofloxacin (although doxycycline can be used) and one or two additional antimicrobials that have adequate central nervous system penetration to help prevent anthrax meningitis (e.g., ampicillin, meropenem, rifampin, vancomycin). The CDC also strongly recommends clindamycin as part to the therapy because of its ability to inhibit protein synthesis, which in theory reduces extotoxin production [12]. The treatment usually lasts 60 days. If a person develops symptoms of the disease or tests positive for the disease itself, antibiotics should be given intravenously for 14 days then orally for the remainder of the 60 days. Supportive care, vigorous hydration, mechanical ventilation, and intensive care monitoring are also necessary.

Despite the swift progression of the disease, mortality rates have been essentially cut in half with the advent of proper antibiotic coverage and invasive ventilation, an option that was not present for anthrax infections at the turn of past century. Recent case studies of inhalational anthrax have all described the use invasive ventilation. None of the case reports explored the role of noninvasive mechanical ventilation as a modality for the acute respiratory failure (ARF) caused by this pathogen. Noninvasive positive-pressure ventilation (NPPV) has been shown to be effective in patients with ARF secondary to chronic obstructive pulmonary disease (COPD) and in noncardiogenic pulmonary edema [13]. Hemodynamic instability and multi-organ failure are contraindications for NPPV, which occurred in all the case studies reviewed.

The studies that most correlate with the effect of NPPV in the setting of inhalational anthrax are trials that discuss the role of NPPV in acute respiratory distress (ARDS), which often is the final stage of this disease. The use of NPPV in ARDS and mass causality respiratory failure has been studied, but the evidence collected cautions about its use because of the lack of efficacy and the potential for complications [14]. Rana et al. showed that 70.3 % of 54 patients presenting with ARDS failed NPPV, and all of the patients who presented in shock eventually required invasive ventilation [15]. A review of the recent case studies involving inhalational anthrax indicated that all patients initially progressed into septic shock, dictating that NPPV would be a poor ventilatory strategy for inhalations anthrax. Further compounding the question of applying NPPV in the face of anthrax-related mass causalities is the concern over NPPV possibly being an "aerosol-producing procedure," which would increase the risk of caregiver inoculation [16]. The evidence for this occurrence, however, is weak and not supported by recent studies from Southeast Asia that studied the role of NPPV in the severe acute respiratory syndrome (SARS) outbreak of 2004 [17].

Despite the lack of evidence, there have been some studies indicating that NPPV has a role in ARF as a bridge to invasive mechanical intubation. It also has a role in weaning patients from extubation. NPPV has the benefits of requiring less sedation and being less expensive, making it an attractive option for ARF in the setting of mass casualties [18, 19]. However, it should be used with caution and as a temporary measure once the diagnosis of inhalational anthrax is suspected.

Regardless of the mode of ventilation, the case studies of inhalational anthrax clearly indicated that continued chest drainage or intermittent thoracentesis played an important role in the management of the patients seen in the 2001 outbreak in the United States [20]. The benefit from aggressive pleural drainage has been recognized and as being due to improvement of the mechanical effects on respiration and in reducing the lethal toxin levels that are believed to be the culprit in the systemic shock caused by inhalational anthrax. NPPV can stabilize the respiratory status until thoracentesis is performed.

In our opinion, use of NPPV can be considered (1) during the prodromal stage of inhalational anthrax, (2) for stabilizing the respiratory status until drainage of the pleural or pericardial effusion, and (3) for assisting in extubation and preventing reintubation.

19.3 Discussion

The role of noninvasive mechanical ventilation in patients with inhalational anthrax is difficult to pinpoint because of the rarity of the disease and the lack of NPPV use in the few cases seen worldwide. Invasive ventilation in such cases occurred in settings geared toward treating ARDS and/or acute lung injury. The hallmarks of ventilation in these cases are low tidal volume settings and high positive end-expiratory pressure, which are difficult to attain or properly measure during noninvasive ventilation. Tidal volumes with NPPV are usually set higher than for invasive ventilators to compensate for leaking and the overall resistance of the patients airway. Lung protective settings are critical to proper ventilation in these patients because of the fragility of lung parenchyma. These limitations make it difficult to manage patients afflicted with inhalational anthrax with NPPV. However, in a setting with mass causalities, nonmechanical ventilation has a role in maintaining ventilation because of its ease of application and its portability.

Key Major Recommendations

- High clinical suspicion and ordering the proper tests to confirm the diagnosis of inhalational anthrax, as well as early initiation of proper antibiotics and ventilation, have been shown to be the key to successful outcomes.
- Frequent drainage of pleural fluid by chest tube or thoracentesis can support mechanical ventilation and decrease the concentration of the lethal factor.
- Lung protective ventilation settings are useful for reducing barotrauma and limiting damage to the lung parenchyma seen in patients with inhalational anthrax.
- NPPV can stabilize the respiratory status during the prodromal stage until drainage of pleural and pericardial fluid can be accomplished. It can also assist when discontinuing invasive mechanical ventilation.

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Noninvasive Mechanical Ventilation in Patients with Hematological Diseases

20

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Keywords
Hematological • Noninvasive mechanical ventilation • Hypoxemic failure

20.1 Introduction

Long-term survival of patients with a hematological malignancy has markedly improved over the last decades, largely because of more effective and more intense therapy. As the respiratory tract is frequently affected in hematological diseases, more patients develop a severe pulmonary complication during the course of their illness. Acute respiratory failure (ARF) is the leading cause of intensive care unit (ICU) admission among hematological cancer patients. Generally, the prognosis is considered to be poor, although there is a trend in recent years toward a higher rate of survival [1, 2].

The aim of intensive care is to support the failing respiratory system and to restore tissue oxygenation while the underlying cause is sought, treated, and reversed. As the need for intubation and invasive mechanical ventilation (IMV) has been identified as one of the cardinal predictors of mortality in this fragile population, interest has been raised for the use of noninvasive mechanical ventilation (NIMV) as a means to avoid intubation. In this chapter, we review the

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evidence regarding the use of NIMV in hematological patients, identify the areas of uncertainty, and provide general recommendations for practical use. We do not discuss the use of NIMV in do-not-resuscitate or palliative care settings.

20.2 Effect of NIMV on Outcome of ARF in Hematological Patients

Studies from the 1980s and 1990s reported mortality rates of 80 % in general hematological patients and 90–95 % in bone marrow transplant recipients needing IMV. In more recent reports, the mortality rates for invasively ventilated hematological patients has decreased to 65–85 %. Despite this improvement, mortality remains unacceptably high [1–3]. As NIMV allows mechanical ventilator support without the disadvantages associated with intubation (e.g., need for sedation, disruption of upper airway integrity with an increased risk for nosocomial pneumonia and airway injury), it has the potential to improve prognosis in hematological patients with ARF.

To evaluate its effect on outcome, NIMV has to be compared with other supportive measures: supplementary oxygen for less profound hypoxemia and IMV for severe ARF. The strategy of providing NIMV, including continuous positive airway pressure (CPAP), to hematological patients with early-stage hypoxemic ARF has been tested against oxygen therapy without ventilator support in three randomized controlled trials (RCTs) (Table 20.1). In a seminal study, Hilbert et al. observed lower intubation and mortality rates in patients assigned to NIMV as compared to treatment with oxygen [4]. Squadrone et al. randomized ARF patients on admission to the ward to receive either CPAP ventilation or oxygen alone. In the CPAP group, fewer patients were referred to the ICU and needed endotracheal intubation or IMV [5]. In contrast, Wermke et al. could not demonstrate a protective effect of NIMV in terms of averting intubation or increasing survival in allogeneic bone marrow transplant patients [6]. The small sample sizes, the large differences in patient characteristics and study settings, and the divergent results preclude firm conclusions about the effect of NIMV versus oxygen, on mortality in hematological patients with ARF.

In the absence of an RCT, the benefit of NIMV over IMV in hematological malignancy patients must be deduced from observational data alone (Table 20.2). Some of the authors identified the use of NIMV as a predictor for ICU survival, but others did not [7]. Because exposure to NIMV is not a random process but the result of a carefully made decision, interpretation of these studies is difficult. Bias may be introduced by the underlying hematological disease and cause and severity of ARF that potentially influence the outcome of NIMV therapy. Gristina et al. showed that after adjustment for propensity to receive NIMV from the beginning, NIMV was associated with a significant lower mortality than IMV [8].

Table 20.1 Randomized controlled trials comparing outcome between hematological patients with ARF treated with NIMV or oxygen only

Study	No. of patients (no. of hematologic patients/no. of bone marrow transplant recipients)	Treatment modalities/setting	Success rate NIMV (%)	Outcome
Hilbert et al. [4]	52 (30/17)	NIVM (pressure support) versus oxygen (Venturi mask)/ICU setting	54	Lower intubation rate and lower mortality in NIMV treated patients
Squadrone et al. [5]	40 (40/17)	cPAP versus oxygen (Venturi mask)/ hematology ward	90	Lower intubation rate and lower mortality in NIVM treated patients
Wermke et al. [6]	86 (86/86)	86 bone marrow transplant recipients	75	Similar intubation rate and mortality in NIMV versus oxygen therapy

Table 20.2 Observational studies comparing outcome between hematological patients with ARF treated with NIMV or IMV

Study	No. of (cancer) patients (no. of hematologic patients)	No. of patients receiving a trial of NIMV/no. of patients receiving IMV as only mode of ventilator support	Success rate NIMV (%)	Outcome
Azoulay et al. [1]	237 (169)	48/189	44	Higher survival in NIMV-treated patients (matched cohort)
Depuydt et al. [2]	166 (166)	26/140	31	No survival benefit in NIMV-treated patients (matched cohort)
Azoulay et al. [3]	203 (184)	79/114	43	Higher survival in NIMV responders
Rabitsch et al. [16]	82 (82)	35/47	31	Higher survival in NIMV responders
Depuydt et al. [7]	137 (137)	30/75	25	No survival benefit in NIMV-treated patients
Gristina et al. [8]	1,302 (1,302)	247/1,028	54	Higher survival in NIMV-treated patients

20.3 Importance of the Cause of ARF in Hematological Patients

The most common clinical presentation of ARF in hematologic malignancy patients is hypoxemia in the presence of bilateral pulmonary infiltrates. This common clinical picture may represent a diverse spectrum of conditions, such as infection, alveolar bleeding, treatment-related toxicity, or direct invasion by malignant cells. The outcome of patients with ARF is, to an extent, dependent on the underlying cause of ARF. Certain conditions such as bacterial sepsis or cardiogenic pulmonary edema are associated with a better prognosis than others such as invasive fungal disease [2, 3]. In addition, patients in whom the cause of ARF remains unclear have a worse outcome than patients with an identified cause [4]. Failure of NIMV is also dependent on the cause of ARF. In a study by Lellouche et al., patients with pulmonary fibrosis, acute respiratory distress syndrome (ARDS), pulmonary embolism, and nosocomial and community-acquired pneumonia had a high failure rate ranging from 40 to 60 % [9].

Consequently, although initial therapy is directed at the immediate management of ARF with ventilator therapy and other supportive care, it is essential that every effort be made to determine the underlying etiology. Fiberoptic bronchoalveolar lavage (FBAL) has traditionally been considered a cornerstone diagnostic procedure in immunocompromised patients with ARF. However, the risk of aggravating hypoxemia in spontaneously breathing patients who already need high fractions of inspired oxygen (FiO_2) is well recognized. NIMV has been used successfully to support oxygenation while performing FBAL. In a recent prospective study of FBAL applied in hypoxemic patients already under treatment with NIMV, only 10 % of patients showed respiratory deterioration possibly associated with FBAL [10]. In a RCT of immunocompromised patients with ARF, Azoulay et al. found that a diagnostic strategy that included FBAL did not significantly lead to more patients requiring intubation than a purely noninvasive strategy. On the other hand, FBAL offered little additional diagnostic information [11]. Based on these data, the decision to perform FBAL must be carefully balanced between the perceived risk of respiratory deterioration leading to IMV versus the benefit of an, albeit limited, increase in diagnostic yield. Although NIMV may allow FBAL to be performed without excessive risk, it seems prudent to omit BAL in profoundly hypoxemic or distressed patients and to rely on noninvasive diagnostic methods that have the least interference with spontaneous breathing.

20.4 Timing and Duration of NIMV and Patient Selection

Despite the potential of NIMV to avert intubation in patients with hypoxemic ARF, it fails in roughly half of the patients (Table 20.1). Mortality among patients requiring intubation after a trial of NIVM is high, and at least one study identified NIVM failure as an independent risk factor for mortality [2]. It is, however, not clear if this high mortality results from harm induced by delayed intubation, or,

alternatively, if it reflects a refractory state of the underlying cause of ARF. Several studies addressed risk factors for NIMV failure in multivariable analyses [8, 12]. In general, patients with greater severity of illness and more profound hypoxemia were more likely to fail a trial of NIMV. In addition, with delayed initiation of NIMV and with prolonged requirement for NIMV, the likelihood of the patient needing IMV increases [12]. These observations, together with the information derived from the RCTs, favor applying NIMV as a trial preferentially during an early phase of ARF, at a time when hypoxemia can still be corrected by supplemental oxygen alone.

In a 5-year multicenter observational study by Gristina et al., the hospital mortality was 66 % with first-line successful NIMV, 80 % with first-line IMV, and 77 % with second-line IMV following NIMV failure. This study not only showed that the mortality associated with first-line IMV in cancer patients is no longer >94 % as shown by studies in the past, it highlights the fact that the mortality rates for second-line IMV after a failed trial of NIMV is similar to that with first-line IMV. This, together with the lower mortality rates in the NIMV success group, encourages the use of a trial of NIMV as first-line treatment for the majority of cancer patients admitted to the ICU with ARF. NIMV success is associated with shorter ventilator days, reduced ICU length of stay, less severe postadmission infections, and lower ICU and hospital mortality rates. It is of note that despite the reduced mortality rates with successful first-line NIMV therapy for ARF in cancer patients, this noninvasive treatment modality is currently underused [8].

20.5 Choice of Ventilation Modality and Interface

As the patient treated with NIMV essentially is awake, patient tolerance of the ventilator support is critical to its success. Although the evidence is largely derived from patients with acute cardiogenic pulmonary edema, it appears that both CPAP and bilevel positive airway pressure are equally effective in correcting hypoxemia. However, no studies have addressed the impact of different ventilator modalities on the success rate of NIMV in hypoxemic patients.

Subjective tolerance of the ventilator mode by the patient may be a more important issue, as is the choice of a well-fitting, comfortable patient–ventilator interface. Over the last decade, facial masks have been developed with improved characteristics, resulting in less leakage and fewer pressure sores. As an alternative to facial masks, the helmet has been heralded as an interface with superior patient tolerance. In a case–control study in immunocompromised patients with hypoxemic ARF, Rocco et al. compared NIMV delivery through a helmet with conventional facial masks and observed that patients in the helmet group required fewer NIMV interruptions and had fewer pressure ulcers [13].

In patients with persistent intolerance of NIMV who would otherwise be subjected to intubation, application of a carefully titrated level of sedation with remifentanil or dexmedetomidine allowed NIMV continuation in 60 % [14, 15].

Although this strategy appeared safe in the closely monitored study setting, it should be used judiciously. A well laid out clinical practice algorithm with indications and contraindications, success and failure criteria for NIMV therapy clearly set out, along with a highly motivated clinical team is crucial for the success of NIMV. Early identification of a patient failing a trial of NIMV is prerequisite to ensure timely institution of a more appropriate therapy, be it IMV or palliative end-of-life care.

Key Major Recommendations

- NIMV is an efficient way to correct hypoxemia in hematological patients with ARF, especially when it is commenced early in the course of ARF and in selected patient groups. The benefit of NIMV over supplemental FiO_2 without NIMV during early ARF after stem-cell transplantation is unclear.
- A trial of NIMV as first-line therapy in hematological patients with ARF appears to be safe provided that contraindications for NIMV are strictly respected and that failure signs of NIMV treatment are recognized early. NIMV should be avoided in patients with profound hypoxemia and in those whose hypoxemia has been present for a prolonged period of time.
- The etiology of ARF should be thoroughly sought. Invasive diagnostic tests seem to provide little benefit over noninvasive tests. Applying NIMV may increase tolerance to fiberoptic bronchoalveolar lavage.

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Noninvasive Ventilation in Patients with Solid Tumors

21

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Keywords
Solid tumors • NIV

21.1 Introduction

During the last two decades, new chemotherapeutic agents, including targeted therapies, and improvement in radiotherapy techniques led to a better prognosis for cancer patients. These new treatments, however, expose patients to various life-threatening complications such as infection, hemorrhage, and drug- or radiation-related toxicity that can require intensive care unit (ICU) admission. The overall survival of oncological patients admitted to the ICU remains disappointing, with recent studies showing mortality rates close to 50 % [1, 2].

Acute respiratory failure (ARF) is the most common cause of ICU admission of cancer patients, most often associated with an infection [2]. The first developed respiratory support, outside of supplementary oxygen, was invasive mechanical ventilation (IMV). The prognosis of cancer patients requiring IMV is poor [3], although improved results were reported recently [4, 5]. A new ventilator support, noninvasive ventilation (NIV), was introduced during the last decade. Today it is considered the initial treatment of choice for acute exacerbation of chronic obstructive pulmonary disease (COPD), acute hemodynamic edema, and hypoxemic ARF in the immunocompromised individual [6]. In most instances, NIV studies did not allow including cancer patients. Thus, even if there is a formal indication for NIV in this population, such as acute exacerbation of COPD or cardiogenic pulmonary edema—reversible situations if correctly handled—the cancer patient in these

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Table 21.1 Studies assessing NIV only in cancer patients

Study	No. of patients with solid tumors	Patients	NIV failure rate	Hospital discharge rate
Auriant [7]	24	Thoracotomy for lung cancer	20.8 %	87.5 %
Meert [1]	28	19 lung, 4 head and neck cancer, 2 breast, 1 ovarian, 1 prostate, 1 gastrointestinal cancer	17.8 %	50 %
Nava [2]	19	10 lung, 3 bladders, 3 digestives, 2 neuroendocrines, 1 kidney cancers	37 %	63 % (ICU discharge)
Meert [9]	57	Mainly lung and breast cancer	31 %	58 %
Azoulay [5]	12			
Meert [4]	16	Mainly lung cancer		
Meert [17]	17	17 solid tumours	23 %	55 %
Cuomo [18]	23	13 lung, 3 stomach, 2 bladder, 2 breast, 2 gut, 1 testicle cancers	43 %	57 %

situations was simply excluded. Furthermore, most studies of cancer patients are concerned with those having hematological malignancies. Hence, the literature dealing with NIV in patients with solid cancer is limited.

The objective of this chapter was to review the studies dealing with the use of NIV in ICU patients with a solid tumor (Table 21.1).

21.2 NIV in Solid Tumor Patients

21.2.1 NIV After Thoracic Surgery

Noninvasive ventilation has been used successfully after thoracic surgery. About a decade ago, Auriant et al. [7] published the first randomized trial about the effectiveness of NIV for ARF after thoracotomy in lung cancer patients. In a small cohort of patients, they demonstrated that treatment of ARF by NIV, in comparison to oxygen only, results in a reduced intubation rate and decreased mortality. Of the 24 patients, 12 (50 %) randomly assigned to the non-NIV group required intubation and IMV versus only 5 of the 24 patients (20.8 %) in the NIV group ($p=0.035$). Nine patients in the non-NIV group died (37.5 %) versus only three (12.5 %) patients in the NIV group ($p=0.045$). As NIV fails in about 20 % of patients, Riviere et al. [8] analyzed episodes of NIV failure in 135 patients after thoracic surgery (97 after lung resection). In all, 40 (29.6 %) of the 135 patients required intubation. Four independent variables were associated with NIV failure during the first 48 h of its use: increased respiratory rate [odds ratio (OR) 4.17 (1.63–10.67)]; increased Sequential Organ Failure Assessment (SOFA) score [OR 3.05 (1.12–8.34)]; number of fiberoptic bronchoscopies [OR 1.60 (1.01–2.54)]; and number of hours spent on NIV [OR 1.06 (1.01–1.11)]. Patients in the NIV failure group had a higher mortality rate (20 % vs. 0 %; $p<0.0001$).

21.2.2 NIV for Acute Respiratory Failure

In 2003, we looked at the usefulness and efficacy of NIV in a feasibility series including 40 cancer patients [1]. Among them 28 presented with solid tumors—mainly lung and head-and-neck cancers. The indications for NIV were hypoxemic pneumonia, hypercapnic respiratory failure, multifactorial respiratory failure, or acute hemodynamic edema. Altogether, 64 % of the patients with a solid tumor were discharged alive from the ICU and 50 % from the hospital.

In 2004, Nava and Cuomo [2] published preliminary data on 19 prospectively recruited solid cancer patients (10 lung, 3 bladder, 3 digestive tract, 2 neuroendocrine, 1 kidney) needing NIV (11 with acute hypoxemic respiratory failure and 8 with hypercapnic respiratory failure). In all, 12 patients were discharged from the ICU after improvement of their condition under NIV. Six of the remaining seven died after undergoing IMV ($n=2$) or suspension of NIV ($n=4$). The survival rates at 6 and 12 months were 42 and 21 %, respectively. These two studies showed that the use of NIV in solid cancer patients is feasible and associated with reasonable short- and long-term outcomes.

Two case-control studies performed in mixed populations with hematological and solid tumors were also published. In one of them, we showed in 94 patients (37 hematological malignancies, 57 solid tumors) that NIV had two significant advantages over IMV for cancer patients with respiratory failure: shorter ventilation duration (3 vs. 10 days, $p=0.001$) and shorter ICU stay (9 vs. 16 days, $p=0.01$) [9]. In the subgroup of patients with solid tumors, NIV resulted in a better prognosis than IMV. The patient were more often discharged alive from the hospital and the ICU in the NIV group than those in the IMV group (69 % vs. 28 %, $p=0.02$ and 58 % vs. 21 % $p=0.01$, respectively). In the other case–control study, Azoulay et al. matched 48 NIV patients with 48 IMV patients and found respective ICU mortality rates of 43.7 and 70.8 % [5]. There were only six patients with a solid tumor in each arm of the study, however, precluding any conclusions for this population.

Noninvasive ventilation efficacy has its limitations. In 2011, we observed in a general population of cancer patients that NIV failure is an independent predictor of poor prognosis, resulting in a higher mortality rate in comparison with immediate IMV (OR 0.30, 95 % CI 0.09–0.95; $p=0.04$) [4]. This retrospective study included 164 patients (106 with solid tumors, 58 with hematological malignancies), among whom 41 (16 solid tumors, 25 hematological malignancies) were treated with NIV before IMV. Only 10 % of patients who failed NIV survived and left the hospital alive. Other poor prognosis factors for in-hospital mortality were found in the multivariate analysis: leukopenia (OR 0.21, 95 % CI 0.06–0.77; $p=0.02$) and elevated bilirubin levels (OR 0.38, 95 % CI 0.16–0.94; $p=0.04$) often reflecting severe multiple organ failure. By extrapolation from studies performed in hematological patients [10–12], we found that some parameters predict NIV failure: the respiratory rate under NIV, longer delay between admission and noninvasive ventilation first use, need for vasopressors or renal replacement therapy, acute respiratory distress syndrome.

21.2.3 NIV in Patients Who Refuse Life-Support Techniques

A few comments should be made on the use of NIV in cancer patients who expressly state that they do not want to be intubated. NIV can be used in two categories of palliative-care patients with solid tumors: patients with do-not-intubate (DNI) orders and patients very near the end of life who accept comfort measures only.

The first study that included cancer patients was done in 11 terminally ill patients who refused endotracheal intubation, including 3 patients with cancer [13]. NIV used to treat ARF was effective in 7 of the 11 patients, all of whom survived and were discharged from the ICU and 5 of whom were discharged alive from the hospital. In another study [14], the same team evaluated 26 patients with advanced disease (3 with lung cancer) who refused intubation. Nine patients died during the ICU stay, including 5 in whom NIV was not effective and was discontinued at the patient's or family's request. In a retrospective study of 233 ICU patients managed with NIV, 36 patients (including 6 with cancer) had DNI orders [15]. The hospital survival rate for these 36 patients was 26 %. A prospective study of patients with DNI orders who underwent NIV showed that this modality was effective in reversing ARF and preventing hospital mortality in patients with COPD or cardiogenic pulmonary edema but not in those with postextubation failure, hypoxemic respiratory failure, or end-stage cancer ($n=40$) [16].

We performed a study specifically in cancer patients with "life-support techniques limitation" including intubation and IMV [17]. Among 87 cancer patients undergoing NIV in the ICU, 18 (20 %) had "life-support techniques limitations" mainly due to advanced cancer status (17 with solid tumors mainly represented by lung cancer). The complications leading to NIV were hypoxemic respiratory failure in 11 patients and hypercapnic respiratory failure in 7. Tolerance to NIV was good. No gastric distension or pneumothorax was described, but some patients had skin redness and irritation over the nose. Only four patients were nonresponders to NIV. Altogether, 14 patients were discharged alive from the ICU and 10 from the hospital. The overall median survival after NIV was 50 days and the 1-year survival was 10 %. Of the lung cancer patients who benefited from NIV, 75 % were discharged alive from the hospital whereas only 16 % of patients with the other tumor types did so.

To the best of our knowledge, only one prospective study [18] evaluated specifically the role of NIV in patients with solid malignancies ($n=23$) receiving palliative care and who were affected by severe hypoxic or hypercapnic ARF. The most frequent causes of ARF were exacerbations of preexisting pulmonary diseases and pneumonia. NIV significantly improved the PaO_2/FiO_2 and the Borg dyspnea score. NIV also improved pH but only in the subset of hypercapnic patients. Of the 23 patients, 13 (57 %) were successfully ventilated and discharged alive, whereas 10 patients (43 %) met the criteria for intubation or died after an initial trial of NIV. Only two of these patients accepted invasive ventilation. The mortality rate in this subgroup was 90 %. A higher Simplified Acute Physiology Score (SAPS II) and a lower PaO_2/FiO_2 on admission were associated with a lower probability of survival. Patients with ARF and end-stage solid malignancies had overall ICU and 1-year mortality rates of 39 and 87 %, respectively. Despite these statistics, there is a consistent subset of patients can be successfully treated with NIV if the cause of the ARF is reversible.

21.3 Discussion

Noninvasive ventilation in solid cancer patients is feasible and effective provided the cause of ARF is reversible and life-extending cancer treatment is available. NIV provides, in comparison with those of IMV, important benefits, such as a reduction in ventilatory support duration and in the ICU and hospitalization stays. Moreover, NIV is associated with reasonable short- and long-term outcomes.

Even patients with advanced cancer and treatment-limitation decisions can benefit from NIV (half of those being discharged alive from the hospital). However, we must take into account the poor long-term prognosis: about 90 % of these patients die within the year, usually from progression of the cancer. This signifies that although cancer status is not a prognostic factor during the ICU stay it recovers its independent influence on survival after resolution of the acute complication [19]. In patients with DNI orders, NIV is well tolerated and prolongs life, allowing further anticancer therapy or giving the patient time to complete life-closure tasks. When provided, NIV must be restricted to situations where ARF is due to reversible causes and for whom potentially life-extending treatments are available. For example, many smokers or former smokers with lung cancer experience COPD exacerbations or episodes of cardiogenic pulmonary edema that may respond promptly to NIV.

For patients who are very near the end of life and who are receiving comfort measures only, NIV may alleviate dyspnea, although there is no evidence that NIV is better than pharmacological treatments such as morphine. Therefore, NIV for palliative reasons is not without controversy. For some authors, the decision to use or not to use NIV is up to the patient and family after information about its risks and potential benefits. Others authors have argued that the ethical and economic costs of using NIV to delay an inevitable death are too high. In all cases, the patient must be fully informed and asked to provide or deny consent. Finally, because of high ICU occupancy, if NIV is to be used in a palliative setting for patients who are close to the end of life, it may be proposed that it be provided in a general ward, given by properly trained staff and the patient carefully monitored.

If the benefits of NIV in solid cancer patients are undeniable, the debate on the correct indication of NIV for ARF in critically ill solid cancer patients is far from being resolved. A prospective randomized control trial is required to evaluate this question adequately.

Key Major Recommendations

- Application of NIV is feasible in solid tumor patients with potentially reversible ARF.
- NIV in solid cancer reduces the duration of ventilation and in-hospital stay.
- NIV failure before IMV is an independent poor prognostic factor in cancer patients.
- NIV is an effective ventilation support for do-not-intubate or palliative cancer patients.

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Noninvasive Ventilation in Patients with Infectious Lung Disease After Solid Organ Transplant

22

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Keywords
Noninvasive ventilation • Infectious lung disease • Solid organ transplant

22.1 Introduction

Solid organ transplantation is a therapeutic option for many human diseases. Liver, kidney, heart, lung, pancreas (including islet cell), and small bowel transplantation have become standard therapy for selected end-stage diseases.

Advances in pretransplant treatment of disease-related organ dysfunction, intraoperative patient management and perioperative care, and improvements in the treatment of rejection have greatly improved the quality of life and survival rates. However, complications such as infections and rejection still affect the recipients in both the short- and long-term course and contribute substantially to increased morbidity and mortality.

22.2 Posttransplant Infectious Disease

Early after transplantation, pulmonary complications associated with variable degrees of respiratory failure and abnormalities of gas exchange appear. They are often the consequences of severe surgical insult, massive perioperative transfusions, occult inhalation of gastric content, elevation of the diaphragm, fluid retention, and atelectases.

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The lungs are particularly vulnerable, representing the main site of infection in lung and heart transplant recipients and the second most common site (following intra-abdominal infection) in liver transplant recipients [1].

It is during the first posttransplant period that the risk of infections is highest because of heavy immunosuppression. The source of an infecting organism can be (1) the donor organ and transfused blood products, (2) reactivation of a previous infection, or (3) endogenous flora or invasive exogenous microorganisms. Nosocomial bacterial infections predominate, as in the general surgical population.

Up to 6 months following transplantation, infectious complications mainly arise from opportunistic pathogens. In the long term, infections are largely due to common community-acquired pathogens (community-acquired bacterial pneumonia).

Respiratory tract infections following transplantation are mostly due to bacteria but are also caused by viruses and fungi. Cytomegalovirus is the most common viral pathogen encountered in all solid organ recipients. Infections due to community respiratory viruses—influenza, parainfluenza, adenovirus, respiratory syncytial virus—typically present as mild, self-limiting upper respiratory tract illnesses.

Aspergillus species are by far the most frequent and lethal fungal pathogens. The incidence of invasive aspergillosis approximates 5 % among the liver, heart, and lung transplant populations. It occurs considerably less frequently following kidney transplantation.

Lower respiratory tract infections are particularly prevalent among lung transplant recipients who have developed the bronchiolitis obliterans syndrome.

Although the incidence of nosocomial pneumonia has declined to less than 10 % in liver and heart transplant recipients, and to approximately 15 % in lung transplant recipients, pneumonia-related mortality remains high [2].

22.3 Noninvasive Ventilation for Treatment of Posttransplant Pneumonia

Respiratory infections after solid organ transplantation are usually associated with reduced lung compliance, increased lung water accumulation, diffuse infiltrates, and consequently deterioration of gas exchange. Because of frequent muscle atrophy, poor nutritional status, and steroid-induced side effects, transplant patients may show limited tolerance to an increased inspiratory workload. If the extra work of breathing can no longer be sustained, respiratory decompensation may ensue and mechanical ventilation may become necessary.

Tracheal intubation and mechanical ventilation for acute hypoxemic and/or hypercapnic respiratory failure complicating hospital-acquired or community-acquired infection are major risk factors for nosocomial pneumonia. The permanence of a tracheal tube is in itself a risk factor for superinfection caused by a multimicrobic flora from the gastrointestinal tract. It is a major cause of posttransplant morbidity and mortality. In immunocompromised patients, the requirement for invasive ventilation has been associated with a relevant negative impact on outcomes [3].

In recent years, a growing interest has emerged in using noninvasive ventilation (NIV) for ventilatory assistance in immunocompromised patients, such as those undergoing bone marrow, liver, lung, cardiac, or kidney transplantation [4]. At our institution, the administration of noninvasive assisted ventilation with positive end-expiratory pressure to treat a temporary graft dysfunction has been adopted for patients in the prone position [5]. Consolidated indications for NIV in these patients include the need to prevent airway invasion, reduce the duration of tracheal intubation, assist the work of breathing in case of potential extubation failure, and (when feasible) continuing intermittent ventilatory assistance in the general ward once the patient has been discharged from the intensive care unit (ICU).

Although there have been no large published experiences with NIV for treating respiratory decompensation of transplanted patients affected by lung infectious disease, the recognized benefits of reducing the possibility of many complications, particularly infections, supports its application [6]. Infectious lung disease requiring readmission to the ICU may occur at any time during the posttransplant course. Some studies have demonstrated variable results with a noninvasive ventilator approach in case of pneumonia and a high failure rate in cases of severe community acquired pneumonia [7, 8]. Even though some data do not support routine use of this technique in patients with severe pneumonia [9], NIV treatment at the first onset of pulmonary infiltrates should be considered a means of preventing alveolar edema and instability in the lung areas close to the exudates. Although the degree of lung involvement cannot be estimated easily, progressive worsening of oxygenation likely reflects marked ventilation/perfusion mismatch due to inflammatory infiltration and edema of the alveolar walls. Prompt institution of NIV, before mechanical ventilation would normally be considered necessary, may alleviate respiratory distress and fatigue.

Whether it eventually avoids intubation, the use of NIV before further deterioration and evident respiratory impairment ensue may lead to reinflation of near-atelectatic lung areas, improved lung compliance, reduced work of breathing, and recovery of arterial blood gas values. Although the results of NIV application in transplanted patients are difficult to predict, and may vary considerably among individuals, it may nevertheless play a role in decreasing pulmonary function impairment and impending hypoxemia. However, if posttransplant pneumonia is associated with acute lung injury or acute respiratory distress syndrome, application of noninvasive methods of respiratory support may be challenging or without significant benefit.

Studies reporting on NIV prevention/treatment as the first-line ventilatory strategy for pneumonia-induced respiratory impairment in immunocompromised transplanted patients are scarce. The potential of NIV to reduce the complications of intubation and mechanical ventilation has been reported by Antonelli et al. [10]. They prospectively compared NIV with standard therapy (supplemental oxygen) in 40 patients with acute respiratory failure (ARF) who had undergone solid organ transplant. Sustained improvement in oxygenation occurred in 12 of 20 patients who underwent NIV compared to 5 of 20 patients with standard therapy ($p = 0.03$). More importantly, the use of NIV was associated with a significantly lower

intubation rate (20 % vs. 70 %, $p=0.002$), severe sepsis and septic shock rate (20 % vs. 50 %, $p=0.05$), length of ICU stay among survivors (5.5 vs. 9.0 days, $p=0.03$), and ICU mortality (20 % vs. 50 %, $p=0.05$). There was no difference in the hospital mortality rate.

The benefits of NIV in preventing tracheal intubation in 21 lung transplant patients admitted to the ICU because of postoperative ARF have been underlined by Rocco et al. [10]. NIV institution resulted in sustained improvement of gas exchange in 15 and avoided intubation in 18 of 21 lung recipients. Other than the three patients who were already diagnosed with pneumonia at study entry (two required immediate intubation), no patient developed pneumonia after entering the study. In the NIV responder group, the rate of complications was low and ICU mortality nil.

In the study by Hilbert et al. [11], the advantages of NIV compared to a standard approach consisting of oxygen administration via facial mask to obtain an $SpO_2>90$ % were clearly demonstrated. The authors randomized a population of immunodepressed patients (including those who had undergone transplantation). They had been admitted to the ICU because of fever, pulmonary infiltrates, resting dyspnea, high respiratory rate and $PaO_2/FiO_2<200$ to undergo NIV (26 patients) versus standard treatment (26 patients). NIV application was associated with a significant reduction in the intubation rate (46 % vs. 77 %), overall serious complications (50 % vs. 81 %), ICU mortality (38 % vs. 69 %), and intrahospital mortality (50 % vs. 81 %). The authors concluded that early application of NIV in immunodepressed individuals with pulmonary infiltrates and ARF led to an improved prognosis. The better outcome was attributed to the lower incidence of nosocomial infections in nonintubated patients. Although these studies did not enroll large populations of recipients, they did suggest an important role for NIV in patients who develop respiratory failure following solid organ transplantation.

If infectious lung diseases are associated with impaired immunity and neutropenia, progression to massive lung involvement and sepsis is often unavoidable. In these cases, mechanical ventilation is mandatory. However, tracheal intubation, indispensable for mechanical ventilation, is a strong predictor of mortality in these individuals. Xia et al. [12] reported that 54 % of liver transplant patients with severe pneumonia needed tracheotomy and mechanical ventilation. The mortality rate of these invasively treated recipients was 37.5 %.

Once under artificial ventilation, the time to remove the tracheal tube becomes important. Rapid extubation of recipients who do not completely fulfill the criteria for safe extubation followed by prompt application of NIV could prevent the loss of vital capacity and impede severe lung de-recruitment following extubation. A NIV trial may be justified even in the presence of the risk of extubation failure. Shortening dependence on the endotracheal tube is particularly desirable for individuals with inflammation and impaired airway ciliary functions, common features of lung infection. By leaving the upper airway intact, NIV can reduce the incidence of bacterial colonization and nosocomial infections.

Once the severity of respiratory failure has been reduced, the feasibility of NIV outside the ICU may decrease the length of permanence in the ICU with the associated potential benefit of preventing further ICU-related crossover infections. Early

implementation of this technique on a general ward (outside the ICU) by a well-trained staff may provide intermittent respiratory support at an early stage of respiratory dysfunction, with satisfactory results when respiratory distress is not severe.

22.4 NIV During Posttransplant Surgical Procedures

Transplant patients may require anesthesia and surgery for various diseases that affect both systemic organs and the transplanted graft. It is expected that anesthesiologists will see more of these patients as life expectancy after transplantation increases and surgical procedures become more frequent. If the recipient undergoes prolonged anesthesia and surgery, lung cell function is impaired, thereby increasing susceptibility to infection. Major changes in respiratory function occur as the site of surgery approaches the diaphragm, especially in debilitated recipients. These changes alter the ventilation/perfusion ratio and may lead to hypoxemia. Prolonged postoperative dependence on an endotracheal tube may damage the tracheal mucosa, increasing susceptibility to microorganism invasion. This situation may be associated with a high mortality rate in immunosuppressed patients. For this reason, rapid removal of a tracheal tube becomes a primary goal even in the setting of nontransplant procedures in patients who had undergone previous transplantation. NIV is a useful alternative to invasive mechanical ventilation and helps prevent complications directly related to the presence of an endotracheal tube. Also, the risk of nosocomial pneumonia is reduced, as is the need for sedation and its consequences.

The expected benefit of NIV is partial compensation for the altered respiratory function by reducing the work of breathing, improving alveolar ventilation, reducing left ventricular afterload with an increase in cardiac output, and reducing atelectases. An unnecessary delay in extubation can potentially significantly increase the risk of respiratory tract infections. Prophylactic application of NIV may be effective in preventing an "incipient" (but not established) postextubation failure.

Conclusion

The decision about whether to initiate noninvasive support in individuals undergoing solid organ transplants and where to apply it (i.e., in a regular ward, ICU, or respiratory care unit) is made by following the indications and contraindications valid for the general population with impending respiratory failure. The pathophysiology of specific disease causing lung dysfunction, the degree of accessory respiratory muscle involvement, and the expertise and skill of the staff should always be considered.

Pneumonia following organ transplantation remains a common life-threatening complication, although the introduction of more effective prophylactic strategies and refinements in immunosuppressive regimens has reduced the severity of infectious complications.

The results of NIV treatment in the management of posttransplant pneumonia are difficult to interpret because of the scarcity of literature, differences in the patient populations enrolled, inclusion criteria, severity of immunosuppression,

and severity of lung disease causing respiratory failure, among others. Rapid withdrawal from invasive ventilation is a crucial target in immunocompromised individuals. NIV is always advisable as the preferred initial ventilatory modality. NIV should not be applied indiscriminantly, however, as an important delay in necessary intubation may significantly increase the risks of adverse respiratory and hemodynamic effects.

Key Major Recommendations

- The lungs are particularly vulnerable and represent an important site of infection following solid organ transplantation.
- Tracheal intubation and mechanical ventilation for acute hypoxemic and/or hypercapnic respiratory failure are major risk factors for nosocomial pneumonia in transplant patients.
- Consolidated indications for NIV in these recipients include the need for preventing airway invasion, reducing the duration of tracheal intubation, assisting the work of breathing in case of potential extubation failure, and continuing intermittent ventilatory assistance in the general ward.
- Noninvasive ventilation treatment at the first onset of pulmonary infiltrates should be considered as a means of preventing alveolar edema and instability in the lung areas close to the inflammatory exudates.
- The results of NIV treatment in the management of posttransplant pneumonia are difficult to interpret, although its potential to reduce the complications of intubation and mechanical ventilation has been repeatedly reported.

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Use of Bronchoscopy in Patients with Pulmonary Infections During Noninvasive Mechanical Ventilation

23

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Keywords
Noninvasive ventilation • Bronchoscopy • Pulmonary infections

23.1 Introduction

Noninvasive ventilation (NIV) refers to the delivery of mechanical ventilation with techniques that do not require an invasive endotracheal airway. Compared with conventional mechanical ventilation (CMV), NIV achieves the same physiological benefits of reduced work of breathing and improved gas exchange. It avoids the complications of intubation and the increased risks of ventilator-associated pneumonia (VAP) [1]. It preserves airway defense mechanisms, speech, and swallowing. It may be used at an early stage to avert the need for endotracheal intubation (ETI) in those patients with respiratory failure and as an alternative to invasive ventilation at an advanced stage of acute respiratory failure (ARF) [2].

Under CMV most of the complications are related to the ETI and to the loss of airway defense mechanisms. Compared with CMV, NIV is associated with a lower risk of nosocomial infections, less antibiotic use, shorter length of stay in the intensive care unit (ICU), and lower mortality [3].

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Fiberoptic bronchoscopy (FB) is a widely performed procedure that plays a crucial role in airway management and simultaneously offers advantages to both diagnosis of airway damage and therapeutic interventions. It may be performed in acute severely hypoxemic and/or hypercapnic patients only after ETI because of the complications associated with the technique. However, FB has been done with diagnostic purposes under NIV to prevent ETI in patients with ARF due to pulmonary infiltrates of unknown origin who are either on spontaneous breathing or under NIV support [4]. FB has also been performed to remove abundant respiratory secretions as in patients with cystic fibrosis treated with domiciliary NIV.

The purpose of this article is to describe the indications of bronchoscopy during NIV concerning pulmonary infections and to describe the technique and procedures.

23.2 Pulmonary Infections in Critically Ill Patients and the Role of NIV

Patients in the ICU are at risk of dying not only from their critical illness but also from secondary processes such as a nosocomial peumonia. Nosocomial pneumonias comprise the second most common hospital-acquired infection, affecting 27 % of all critically ill patients admitted to the ICU. Furthermore, 86 % of these cases occurred in patients while on CMV called VAP [5].

Patients undergoing CMV in ICUs have a 1 % chance per day of acquiring VAP. VAP is the most frequent ICU-related infection in patients requiring mechanical ventilation. In contrast to the other less life-threatening ICU-related infections, the mortality rate for VAP ranges from 20 to 50 %. These clinically significant infections prolong duration of CMV and length of stay in expensive high-intensity care settings (i.e., ICUs). They therefore have a great impact on health-related cost. A key role in the pathogenesis of VAP is the positioning of the artificial airway. The presence of an endotracheal tube (ETT) allows microorganisms to have direct access to both the ICU environment and the tracheobronchial tree, thereby bypassing all the defense mechanisms situated above the vocal cords. The ETT itself can contribute to the pathogenesis of pneumonia by allowing direct entry of bacteria into the lung and by providing a surface for the formation of a bacterial biofilm along the inside of the ETT. As a matter of fact, VAP has been better renamed as ETI-associated pneumonia [6]. Furthermore, CMV exacerbates both pulmonary and systemic inflammation in response to bacteria without necessarily affecting bacterial clearance or extra-pulmonary bacterial dissemination [7].

However, the definition of VAP is not clear. Some authors have proposed wider definitions and conclusions, stating that VAP is not due to the ventilator but to the coincidence of several factors (e.g., tubes, high likelihood of aspiration of nasal and oropharyngeal secretions, presence of an underlying morbidity, impairment of the local and systemic host defenses).

Institution of timely and appropriate antimicrobial therapy is crucial to decreasing the complication and mortality rates related to VAP. An important challenge for clinicians who deal with lower respiratory tract infection is how to diagnose severe infections and tailor the appropriate therapy in critically ill patients. There is a higher chance of mortality if the patient receives inadequate therapy for whatever microorganism is recovered. Moreover, the mortality rate for patients given inadequate therapy was higher than that for patients with acute respiratory distress syndrome (ARDS) or sepsis. Choosing the initial empirical antibiotic may bee difficult because of the still rising incidence of multi-drug-resistant pathogens.

The difficulty of the microbial investigation is to obtain the sample from the lower respiratory tract without contamination with upper airway colonizing microbial flora. Optimal techniques for obtaining appropriate respiratory samples remain controversial.

Diagnosis of pneumonia is an important part of the management of VAP. After identifying the etiological agent(s), the choice of antimicrobial drugs is much easier in light of the susceptibility pattern of the causative pathogens [8].

In this context, the role of NIV assumes increasing importance. Compared to CMV treatment, early use of NIV could be helpful in the ICU to reduce pulmonary infective complications. This is especially true in ARF patients with high vulnerability to nosocomial infections, such as those with reduced immune defense mechanisms. Hilbert et al. extended the application of NIV to immunosuppressed patients with pulmonary infiltrates, fever, and ARF, with nearly half of the cases secondary to nosocomial pneumonia [9]. There was a significant reduction in the incidence of ETI and CMV in the NIV group compared to the control group. Similar findings have been reported in patients with acquired immunodeficiency syndrome. Preventing ETI and CMV in these patients with reduced immune defense mechanisms had a marked influence on mortality, which is largely explained by the prevention of VAP [9].

The appearance of VAP during NIV is a rare complication. Airway colonization by nonfermenting Gram-negative bacilli is strongly associated with NIV failure. Because it occurs before intubation, however, it would be a marker rather than a consequence of NIV failure necessitating intubation.

Immunocompromised patients undergoing NIV should be carefully treated under strict monitoring in the ICU or a respiratory high-dependency unit (RHDCU), where ETI and invasive ventilation are promptly available. Note, however, that NIV is not appropriate for all immunocompromised patients as nosocomial infections associated with severe hypoxemia and nonpulmonary organ dysfunction are likely to fail under NIV.

Major risk factors for NIV failure in immunocompromised hematological patients were the severity of the illness at baseline and the presence of ARDS on admission. ETI should be an early alternative in patients remaining tachypneic under NIV or who have severe hypoxemia ($PaO_2/FiO_2 < 200$). Early recognition of carefully selected ARF patients who are likely to benefit from NIV and their timely referral to the ICU or RHDCU are critical issues for NIV success [10].

During the era of severe acute respiratory syndrome and the H1N1 pandemic, the chance of transmitting infection from patients undergoing mechanical ventilation to clinicians, nurses, and therapists should be considered. According to in vitro studies, the use of NIV to treat severely contagious lung infections theoretically exposes health care workers to the risk of contamination via the spread of infectious droplets [11]. Consequently, similar to the precautions established for other aerosol-generating procedures (i.e., nebulization, high-flow oxygen therapy) clinicians must follow recommendations to prevent spread from infected patients (i.e., in regard to the individual protective devices) during management of NIV. Recently this NIV-related risk of contamination has been re-dimensioned by an elegant in vivo study [12].

23.3 Fiberoptic Bronchoscopy and NIV

Fiberoptic bronchoscopy is commonly used in ICUs and RHDCUs. It plays a crucial role in the management of the critically ill respiratory patient admitted to an intensive care hospital setting because of its diagnostic and therapeutic applications. In hypoxemic patients with newly diagnosed pulmonary infiltrates, FB may be of "additional value" but is potentially risky. Accordingly, the fact that patients requiring FB during ICU stay have a high mortality rate is interpreted as a "surrogate" indicator of the presence of severe pulmonary dysfunction.

Although FB is generally considered a safe and effective procedure, it is not devoid of risks. The bronchoscope occupies 10–15 % of the tracheal lumen and decreases the arterial oxygen pressure (PaO_2) by 10–20 mmHg during and up to 2 h after the procedure. This interval may cause respiratory complications or cardiac arrhythmias. The American Thoracic Society therefore recommends avoiding FB and bronchoalveolar lavage (BAL) in patients with PaO_2 levels that cannot be corrected to at least 75 mmHg or to an arterial oxygen saturation (SaO_2) of >90 % with supplemental oxygen [13]. In these patients, the traditional alternatives were either intubation and CMV to ensure adequate ventilation during FB or application of empirical treatment.

Pathophysiological changes in respiratory mechanics should be borne in mind during FB in patients on CMV. Insertion of a bronchoscope into the ETT can lead to a relevant decrease in tidal volume and large increases in the peak inspiratory pressure. When performing FB during CMV, the inside diameter of the ETT should be at least 2.0 mm larger than the outside diameter of the bronchoscope to maintain adequate volume delivery and minimize incomplete emptying of the lungs (i.e., development of auto-positive end-expiratory pressure). In spontaneously breathing young children, FB was associated with decreases in the tidal volume and respiratory flow, which were reversed by applying continuous positive airway pressure (CPAP).

NIV is considered as a valid tool to prevent intubation in spontaneously breathing patients who do not still require a ventilator support. This is, especially true in immunosuppressed patients and critically ill patients with ARF as well as in chronic obstructive pulmonary disease (COPD) decompensated patients due to community-acquired-pneumonia (CAP) with hypercapnic encephalopathy and

excessive respiratory secretions [2, 14]. Baumann et al. demonstrated that FB could be performed in patients with severe hypoxemic ARF who are already on NIV support, underlying the need for physicians to have adequate experience with bronchoscopy and ETI [15].

23.3.1 Technique

As is recommended for spontaneously breathing patients, the thinnest possible bronchoscope compatible with successful performance of the procedure should be used. FB during NIV should be closely monitored in an ICU. The patient needs at least 15–20 min to adapt to the NIV [16]. After FB, NIV has to be maintained with the same parameters for at least 15–90 min, depending on the clinical evolution of the patient [17].

If CPAP is used, it is recommended that it be set initially at 5 cmH_2O [17]. When using a bilevel positive system, initial inspiratory and expiratory positive airway pressures of 14–15 cmH_2O (IPAP) and 5 cmH_2O (EPAP) are considered. Alternatively, pressure-support ventilation set at 10 cmH_2O can be used [16, 18, 19].

During FB, the FiO_2 should be initially kept at 1.0 and then adjusted to a level able to maintain $SpO_2 > 92$ %. The rest of the parameters include a spontaneous/cycled mode with a mandatory inspiration rate of 4–8/min and a inspiration/expiration relation of 1:2—except in special cases (1:3 in patients with severe end-expiratory lung volume or 1:1 in restrictive cases)—to achieve effective ventilation (expiratory tidal volume 8–10 ml/kg and a respiration rate < 25 breaths/min) [20].

In the case of hypoxemia, the EPAP can be increased by 2-cm increments until the SpO_2 is >90 %, trying not to exceed limits that might generate patient intolerance or gastric distension. Increasing IPAP is recommended (maximum 25 cmH_2O) to avoid or relieve hypercapnia while adjusting the EPAP to avoid rebreathing.

Fiberoptic bronchoscopy may be performed via the oral or nasal route, depending on which mask is used. Other techniques of NIV-facilitated bronchoscopy have been reported. Heunks et al. modified a total full-face mask by inserting a synthetic plastic cylinder that was secured in the mask at a position that allowed introduction of the bronchoscope through the mouth without interfering with the ventilator circuit [21]. When NIV is delivered through a facial mask, a T-adapter is attached to the mask for insertion of the bronchoscope through the nose. A facial mask permits use of both oral and nasal insertion (Fig. 23.1). Chiner et al. used the oral route with a mouthpiece closed by an elastic membrane through which the bronchoscope was inserted and which acted as a retention valve for administration of pressure [22]. If a helmet is used, the bronchoscope is passed through the specific seal connector placed in the plastic ring of the helmet.

Patient discomfort must be minimized during FB. Topical anesthesia of the nasopharynx and larynx with lidocaine reduces cough and helps the advance of the

Fig. 23.1 When NIV is delivered through a facial mask for insertion of the bronchoscope, both via oral or nasal routes are permitted

bronchoscope into the tracheobronchial tree. Some authors do not administer pharmacological sedation, whereas others use midazolam or propofol to reduce patient discomfort without causing any significant adverse effects or increasing the ETI rate.

The contraindications to bronchoscopy in a patient on NIV are the same as for any NIV application. They include conditions resulting in high aspiration risk or inability to protect the airway, psychomotor agitation, ARF caused by status asthmaticus, the presence of facial deformities, and recent oral, esophageal, or gastric surgery [17, 23]. Contraindications to FB itself include acute cardiovascular disease, thrombopenia of <60,000, or prothrombin activity less than 60 % if any bioptic technique is thought to be done.

In contrast to other bronchoscopic techniques used for microbiological diagnosis in critically ill patients, bronchoaspiration, BAL, and protected brush specimens are preferred in patients undergoing NIV [24]. The BAL technique differs among authors, but they all include sequential instillation and retrieval of three to six aliquots of 30–50 ml of physiological saline solution [17, 19, 25].

Because of the high rate of complications associated with transbronchial lung biopsy in ventilated versus nonventilated patients, one should carefully balance its risks against its benefits.

In summary, performing FB in critically ill, unstable, ventilated patients in a safe manner requires knowledge of the specificities of such a setting. FB should be performed only by bronchoscopists or pulmonologists with specific training in this area.

Key Major Recommendations

- The use of NIV during FB should be considered mainly because of the risks connected with ETI in critically ill patients who are still on spontaneous breathing or on NIV support.
- It is strongly recommended that only those with competence and expertise in both bronchial endoscopy and noninvasive positive-pressure ventilation should perform NIV-assisted FB. Also, the team should be competently trained regarding emergent intervention, included cardiopulmonary resuscitation and ETI.
- General contraindications for NIV and FB should be considered prior to the procedure.
- Close monitoring is needed before, during, and after FB. NIV should be maintained for at least 2 h after bronchoscopic procedures.

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Noninvasive Ventilation in Patients with Major Burn Injuries

24

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Keywords
Burns • Ventilator Associated Pneumonia • Inhalational burns • Intubation • Extubation • Facial Burns • Noninvasive ventilation • Helmet

24.1 Introduction

Severe burns are one of the most devastating forms of trauma. In South Africa, burn injuries are the third commonest external cause of fatal injuries up to the age of 15 years and the main cause under the age of 4 years. In the Cape Town region, at least 6 in 10,000 children are seriously burned every year, and as many as 15 in 10,000 toddlers and infants [1–3]. The majority of pediatric burns are scalds sustained in the domestic setting, whereas most burns in adults and the more severe burns in children are caused by flames. These burns are most common in informal housing as a result of the use of paraffin stoves for cooking and heating. Other prominent causes of flame burns in adults include accidents in the workplace and as a result of epilepsy or interpersonal assault. Burn victims caught in enclosed spaces are frequently the most severely injured, and those who suffer smoke inhalation injury may have mortality rates over 30 % [4, 5].

A number of advances have been made in recent times with regard to fluid resuscitation protocols, dressings, infection control strategies, antimicrobials, surgical

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Table 24.1 Factors predisposing burn patient to pneumonia in the ICU

Factor	Mechanism
Intubation (especially pre-hospital/emergency)	Bypass glottis barrier; pooling, leak of, and inability to clear secretions
Cutaneous thermal injury	Bacterial reservoir; systemic inflammation; immunosuppression
Prolonged ventilation	Sustained microaspiration; secretions; reintubation
Inhalational injury	Direct injury; exudate formation; poor mucociliary clearance; reduced lung compliance; ARDS; prolonged ventilation
Transport out of ICU (e.g., to theater)	Reintubation; bacterial translocation
Blood transfusions	Immunosuppression

ICU intensive care unit, *ARDS* acute respiratory distress syndrome

techniques, intensive care, and nutrition. There is now widespread recognition that specialist burn units or centers deliver the best care for these patients. As a result of these measures, mortality and morbidity rates have declined significantly over the last few decades [3, 6, 7].

The main challenge to those managing major burns is avoiding the threat of overwhelming infection. Because significant thermal injuries induce a state of immunosuppression and the wounds themselves are exposed to microorganisms prior to skin graft coverage, three-fourths of all severe burn-related deaths are as a consequence of infection. In addition to burn wound infections, they may manifest as sepsis or pneumonia, many of which cases are nosocomial. There are a number of mechanisms for the development of pneumonia in those severely burned (Table 24.1). Pulmonary complications are common with inhalational injury, but burn patients have more pulmonary complications even without direct lung injury. Atelectasis and hypostatic pneumonia are common owing to altered ventilation and reduced lung expansion that may occur in patients with chest or abdominal burns. These patients may also have a high risk of aspirating, and respiratory physiotherapy with regular airway suctioning of upper airway secretions and expectoration of sputum may be critical to maintaining pulmonary function [3, 8, 9].

The overwhelming systemic inflammation associated with a major burn may result in respiratory compromise itself, manifesting as acute respiratory distress syndrome (ARDS). Lower respiratory infection in the presence of major burn injury carries an additive mortality of 60 % [5].

Those who require prolonged ventilation are at risk of developing ventilator-associated pneumonia (VAP). VAP is responsible for significant morbidity and mortality and ranks as the second commonest hospital-acquired infection. A large European trial in a variety of pediatric settings showed that VAP accounted for more than half of all hospital-acquired infections in pediatric ICUs. The prevalence of nosocomial pneumonia in the ICU ranges from 10 to 65 %, and mortality rates exceed 25 %. Those who develop VAP are twice as likely to die compared to those without VAP, and they spend longer in intensive care. In addition, the nosocomial bacteria that cause VAP tend to be more resistant to treatment [10].

Table 24.2 Strategies to prevent ventilator-associated pneumonia in burn patients

Reduce the duration of ventilation
Postpyloric feeding
Chlorhexidine mouthwash
Reduce transfusions
Head elevation
Selective decontamination of the GIT
Staff factors: hand hygiene and barrier nursing
Silver endotracheal tubes and continuous aspiration
Noninvasive ventilation as adjunct to extubation

GIT gastrointestinal tract

The incidence of VAP in major burns in our setting is as high as 30 cases per 1,000 ventilator days, which is more than double that in any other category of ventilated patients. A protocol has been implemented to reduce the incidence of VAP. Some of these preventive strategies are listed in Table 24.2. Undoubtedly the most effective strategy has been to reduce the duration of ventilation [3].

Critical to managing patients at risk is a reduction of secondary insults inherent in management strategies. Endotracheal intubation/mechanical ventilation has been the mainstay of treatment for apparent or impending respiratory failure in patients with major burns. In fact, more than three-fourths of inhalational burn victims require some form of respiratory support [11]. Other than VAP, there are significant potential complications inherent in intubation and mechanical ventilation. During the process of intubation, up to 20 % of patients experience a period of hypoxemia, 10 % are hypotensive, 7 % undergo esophageal intubation, and 6 % aspirate. Other complications include dental injury or inadvertent extraction, swallowing dysfunction, dysphonia, and tracheal stenosis. Repetitive laryngeal barotrauma can result from suction catheter use for clearing secretions [12, 13].

Some authors have suggested that the features used to guide physicians have overstated the need for invasive ventilation, particularly in the hospital setting. Emergency intubation at the scene of the fire, with its high complication risk, should be avoided whenever possible. Clinical features discovered in the history and physical examination—so-called soft signs (singed nasal hair, closed space fire, facial burns) and hard signs (stridor, hoarse voice, dysphagia) used to guide physicians to intubate and ventilate burn victims—may be less helpful than traditionally taught, in respect to their accuracy for determining the actual need for ventilation. This is particularly relevant in light of the risks involved and the possibility of an effective alternative to invasive airway management [12, 14].

For fire-related deaths, the toxic products of combustion are probably more important a cause of morbidity than the airway thermal burn itself. The effects of direct thermal burns in the oropharynx are analogous to those changes occurring elsewhere in the body. Protein is denatured, activating the complement cascade—histamine, xanthine oxidase, oxygen free radicals—which are responsible for further protein extravasation and edema. Toxins and inhaled products interfere with the normally effective methods for clearing the upper airways. In the trachea and bronchi, ciliated epithelium and mucus-secreting epithelium normally make up the

"mucociliary escalator," which is capable of removing inhaled particulate matter at a rate of up to 4 cm/h. Mucosal necrosis and slough leads to impaired clearance and airway obstruction. The presence of a cuffed endotracheal tube may itself further interfere with this mucociliary elevator. Bronchoconstriction and mucosal sloughing may result in atelectasis, with possible progression to pneumonia [12, 15, 16].

24.2 Noninvasive Ventilation for Major Burn Injuries

The International Consensus Conference in Intensive Care Medicine [17] defined noninvasive positive-pressure ventilation (NIPPV) as any form of ventilatory support that does not use an endotracheal tube. Its goal is to decrease the work of breathing, optimize ventilatory exchange, and avoid intubation. Typically, NIV is positive-pressure ventilation with the use of a face mask attached to a ventilator. CPAP masks are widely used for improving oxygenation in hypoxemic patients and to rest patients with chronic disorders such as COPD or neuromuscular disorders. The benefits of NIPPV are most often described for avoiding reintubation (by > 50 %) after exacerbation of COPD. As a result, mortality and hospital length of stay have decreaased. Recognizing the benefits of NIV, clinicians have attempted NIV and adapted its use for managing acute reversible respiratory failure in addition to the traditional uses. NIV has seldom been used in the context of burn patients, but it has been shown to be an effective means of oxygenating awake and alert surgical and injured patients.

The principal benefit of NIV is the avoidance of intubation and its concomitant complications. There are a number of additional benefits in avoiding intubation in the burn patient. Nonintubated patients maintain better oral hygiene and gut function (they may be able to continue with standard oral intake), which are critical components in the management of major burn victims. Few other categories of critically ill patients undergo such profound catabolism. Nonintubated patients also communicate better and require minimal sedation. This is important because burn patients can expect to be in hospital at least 1 day per percentage of body surface injured, which usually translates to lengthy periods away from "normal" society, making reintegration challenging. Further benefits are listed in Table 24.3.

Ventilator-associated pneumonia is the most feared complication of endotracheal intubation, particularly in burn patients, who are inherently more susceptible to infection in light of the overwhelming systemic inflammation and because normal

Table 24.3 Benefits of noninvasive ventilation

Improved communication
Better oral intake and gut function
Maintain oral hygiene
Avoid orotracheal injury and barotrauma
Fewer respiratory tract infections
Maintain protective mechanisms
Less sinusitis
Shorter ICU and hospital stays
Improved speech and swallowing after extubation

defense mechanisms are bypassed (skin, gut, sinuses, orotracheal area). NIV has been shown to reduce the incidence of VAP, predominantly by reducing the period of ventilation and by maintaining intact airway protection mechanisms. Shorter ICU stays are also independently related to improved survival and translate into significant cost benefits for the health system [18, 19].

Success with NIV has traditionally been achieved only under certain circumstances. The patient must be cooperative, able to protect his or her own airway, and have an intact cough reflex and adequate secretion clearance. Uncooperative patients may repeatedly remove their mask, ventilate out of synchronization with the ventilator, or may not remove their mask in the event of vomiting, placing them at risk for aspiration. Hemodynamic instability has been a relative contraindication for the use of NIV. Patients who cannot obtain an adequate seal are excluded, as are patients with gastrointestinal trauma or obstruction requiring nasogastric intubation and who are at risk for vomiting. Aerophagia may also occur, particularly if the pressures used to ventilate are >30 mmHg, which would overcome the closing pressure of the lower esophageal sphincter. This is particularly important in those with underlying gastrointestinal dysfunction or stasis, as is often the case in patients with major burns [12, 20].

Although there is a paucity of literature describing the use of NIV in burn victims with or without inhalational injury, its use ought to be considered in selected patients who meet the criteria for its use. Inappropriate use of NIV in burn patients can be catastrophic. This patient population is already at greater risk for hemodynamic instability and respiratory infection than other cohorts. Also, analgesic requirements may result in levels of sedation mitigating against the use of NIV.

Smailes was able to reduce the incidence of endotracheal reintubation to 7 of 30 burn patients with respiratory dysfunction after extubation [21]. In a 6-year review of the use of NIPPV as an adjunct to extubation, 104 extubated pediatric burn patients were studied. Only 15 % required reintubation. Ten patients who experienced respiratory distress after extubation received NIPPV support. Four of them required reintubation for worsening respiratory status. The other six patients avoided it [22].

More work has been done in patients with trauma indications other than burns. In a study by Linton, patients with blunt chest trauma were treated with either intubation and ventilation or NIV with CPAP. The two groups had similar positive end-expiratory pressure (PEEP)/CPAP levels, patient age, and incidences of rib fractures, flail chest, and pulmonary contusion. The CPAP group had a smaller number of tracheostomies, fewer ICU days, and fewer complications [23]. In a further study, Hurst reviewed trauma victims with blunt chest injuries (rib fractures, pulmonary contusion, flail chest), penetrating chest injuries, and long bone fractures. CPAP was used in 33 alert patients with hypoxic respiratory failure. The mean duration of CPAP was 28 h. Only two patients (6 %) required intubation for failure of oxygenation but not ventilation [24].

Extrapolated to the intubated burns patient, earlier extubation and NIV application may decrease patient discomfort, sedation, ICU stay, morbidity, cost, and mortality. NIV may prove to be a useful adjunct, allowing early extubation and providing bridging ventilatory support until normal respiration returns. In the context of an acute major burn injury, it is rational to consider NIV (prophylactically) for the patient with high carbon monoxide blood levels, one who is receiving significant

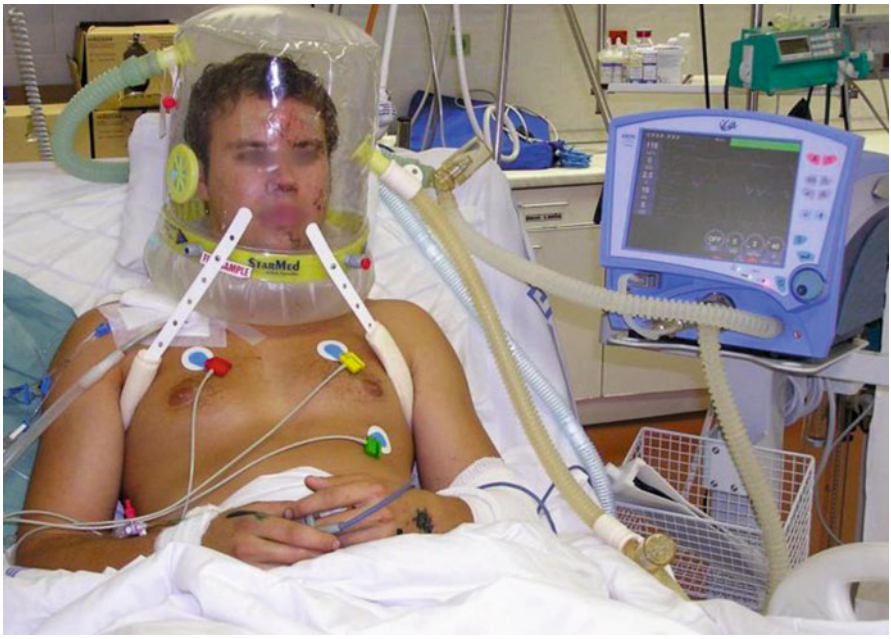

Fig. 24.1 Hermetic plastic helmet with continuous positive airway pressure in use (Castar, Starmed, Italy)

fluid volumes, or another who has history or examination features that suggest an inhalational injury but who may not require intubation. Clearly, this represents a paradigm shift from the traditional teaching of early intubation in at-risk patients. However, one must be cogniscent of the fact that these patients are in a high-care setting and are awake, alert, and cooperative on initiation of NIV. The process of NIV would have been clearly discussed with them. Any deterioration may warrant switching to intubation and mechanical ventilation in a controlled environment.

On initiation of NIV, low levels of PEEP are applied. Once the patient is comfortable, the device is secured and set to minimize the work of breathing (assessed by accessory muscle use, rate of respiration, tidal volume, and patient comfort). Arterial blood gases, pulse oximetry, and end-tidal CO_2 should be monitored regularly.

One of the major criticisms of NIV is related to patient intolerance, particularly in the context of facial burns. If the interface contributes to excessive pain, discomfort, or claustrophobia for the patient, the benefits of NIV may be lost. The patient is then more likely to require intubation and mechanical ventilation. Optimal use has required a firm seal to maintain the pressure administered. Certain devices have resulted in skin necrosis over the bridge of the nose or zygoma if worn for extended periods. Pressure sores occur in up to 10 % of patients undergoing NIV. In patients with facial burns, this is unacceptable. Duoderm (Convatec, Skillman, NJ, USA) or a similar product may ameliorate these effects in some cases.

As a result of problems with face-mask NIV, helmets (Fig. 24.1) have been devised for this purpose [12, 25]. Several studies have demonstrated its benefits,

including improved comfort and ability to interact while reducing the likelihood of superadded cutaneous trauma where the equipment is secured, particularly in burn patients. Criteria for helmet use are similar to standard NIV principles. Better tolerated, helmet NIV has been shown to be as effective as conventional face mask NIV in reducing hospital stay, mortality, infectious morbidity (including pneumonia), and the need for invasive ventilation. Uncontrolled leaks are significantly less likely with helmets than with traditional face mask methods. The only concern relating to helmet NIV has been its inability to maintain PCO_2 levels, probably as a result of CO_2 rebreathing. Factors relating to patient–ventilator interaction may also need to be monitored more closely in patients undergoing helmet NIV [12, 25].

Key Major Recommendations

- Noninvasive ventilation is an important potential means of avoiding intubation in major burn victims.
- It may also be utilized to maintain airway patency after extubation.
- It is important that patients considered for NIV meet the criteria for its use and be monitored appropriately.
- Transparent helmets have been designed and have shown to be as effective as traditional face mask interfaces. They may be applied more successfully in patients with facial burns.
- Prospective, randomized studies may better elucidate the role of NIV in burn patients with inhalation injury.

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Part III

Clinical Indications in Pediatrics

Infant Nasal Bubble Continuous Positive Airway Pressure in Resource-Limited Settings

25

Andrew G. Smith and Eric D. McCollum

Keywords
Bubble CPAP • Resource-limited • Infant • Respiratory failure • Pneumonia

25.1 Introduction

Respiratory disease, including pneumonia, is the leading cause of mortality in the developing world for children under 5 years of age [1]. Integrated Management of Childhood Illness (IMCI) guidelines address pneumonia by focusing on clinical diagnosis, empirical antibiotic treatment, and oxygen therapy for children who are either hypoxemic or demonstrate clinical signs of respiratory distress [2]. Neither IMCI guidelines nor the World Health Organization's Hospital Care for Children discusses advanced ventilatory strategies [3]. Thus, evidence supporting the use of noninvasive or invasive ventilation in resource-constrained settings is limited.

25.2 Patient Selection

25.2.1 General Indications

Bubble continuous positive airway pressure (CPAP) was developed during the early 1970s for use in premature infants but was largely replaced by mechanical

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Table 25.1 Suggested nasal bubble CPAP eligibility and weaning criteria

Eligibility criteria
Age < 12 months *and* either of the below criteria
Hypoxemia (e.g., oxygen saturation <90 %) *despite* oxygen supplementation
Mental status changes associated with severe respiratory distress characterized by grunting, severe supracostal retractions or head nodding by the infant, or severe indrawing of the lower chest wall
Weaning criteria
Able to maintain oxygen saturation > 90 % off CPAP and with supplemental oxygen only
Improved mental status
Improved respiratory effort

CPAP continuous positive airway pressure

ventilation over subsequent years [4]. Recently, there has been a resurgent interest in bubble CPAP among health care providers in both resource-rich and resource-limited settings [5]. Although most of the current evidence is associated with bubble CPAP use in neonates, especially premature neonates with respiratory distress syndrome, its indications are evolving beyond the neonatal period. For example, we primarily used bubble CPAP in older human immunodeficiency virus-infected African infants with respiratory failure secondary to presumed *Pneumocystis jirovecii* pneumonia [6] but also in infants with severe respiratory distress due to other causes such as viral bronchiolitis, bacterial pneumonia, and pulmonary edema due to aggressive fluid resuscitation, heart failure, or acute respiratory distress syndrome states associated with sepsis, malaria, and other conditions. See Table 25.1 for suggested eligibility criteria.

25.2.2 Other Medical Considerations

As with all noninvasive modes of ventilation, patients must be able to protect their airway and have an intact respiratory drive. Ideal candidates are also hemodynamically stable, with their disease largely limited to the respiratory system.

25.2.3 Age Recommendations

While the evidence is limited regarding age, we generally suggest the use of bubble CPAP for a younger age range (i.e., 0–12 months) (Table 25.1). We recommend this age range in part because resource-limited settings often suffer from severe staffing shortages, and older infants require higher levels of supportive care or sedation to ensure that the CPAP device remains intact on the patient's face. This higher level of supportive care often requires more attention than is possible in some facilities. Other strategies to keep the device on the infant include restraints and/or teaching the caregiver to identify when the device is misplaced and alerting the health care staff.

25.3 Equipment and Design

Bubble CPAP requires relatively few supplies. Our design requires an oxygen concentrator as the primary source of oxygen delivery, although an oxygen cylinder is an acceptable alternative. The key feature of either delivery system is maintaining an adequate, consistent flow. To achieve minimum oxygen flow, *one* oxygen concentrator or cylinder must be dedicated to *one* CPAP circuit only. Additional supplies include nasal prongs that can be affixed to the patient to eliminate any air leak, a humidification device, and a reservoir filled with sterile normal saline.

We used Hudson nasal prongs (Hudson RCI, Research Triangle Park, NC, USA) attached to a humidified oxygen concentrator with a flow of 4–5 L/min. The prongs are available in sizes that fit a range of patients from extremely low birth weight infants to those 12–24 months of age. The Hudson prongs also come with inspiratory and expiratory elbows and can be sterilized for safe reuse. The right angle elbows allow for a secure fit to the infant's face. Corrugated tubing is then connected to the expiratory elbow of the nasal cannula, with the other end secured into a sterile normal saline reservoir. This setup creates a closed respiratory system capable of generating constant expiratory pressure. The depth of the tubing in the saline reservoir determines the amount of positive end-expiratory pressure (PEEP) supplied. We are easily able to achieve a PEEP of 5 cmH_2O if the nasal cannula creates a good seal with the infant's nares (Fig. 25.1). We partially fill the oxygen

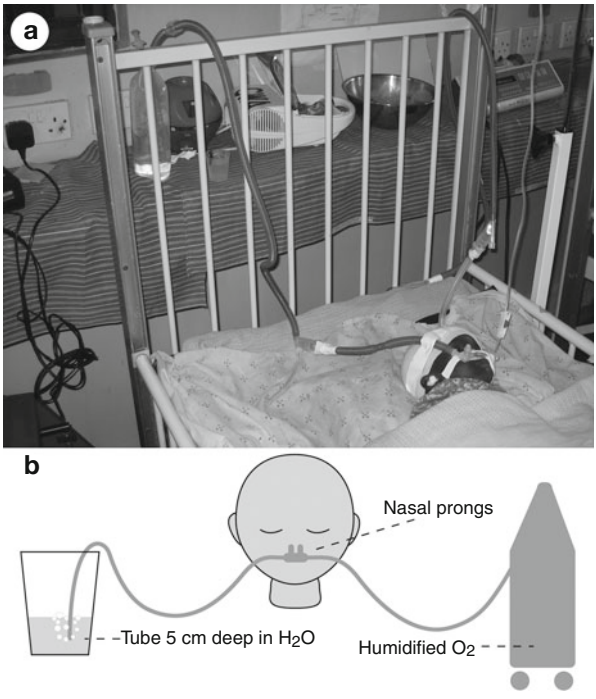

Fig. 25.1 (**a**) Four-month-old HIV-infected infant with presumed PJP supported using bubble CPAP (**b**). Schematic of simple bubble CPAP design

concentrator bottles with water so the delivered oxygen is humidified. A 500-mL or 1-L sterile normal saline intravenous fluid bottle serves as the reservoir.

25.4 Supportive Care

The key to the success of bubble CPAP is competent, detail-oriented supportive care. We hospitalize bubble CPAP patients to a high-dependency unit (HDU) ward with 24-h nurse coverage. The patient-to-nurse ratio is not more than six patients to one nurse. Ideally, nursing care involves an even smaller patient-to-nurse ratio if resources are available.

There are two significant issues regarding nasal bubble CPAP in infants: keeping nasal passages clear of secretions and maintaining an adequate nasal seal. The underlying disease process often contributes to increased secretions. Additionally, inadequate humidification of oxygen flow promotes dry secretions, which can lead to nasal obstruction. Frequent suctioning is often required to keep nasal passages clear, but overly aggressive suctioning can lead to unintended mucosal swelling or bleeding that can also obstruct the nares. Importantly, bubble CPAP if effective only if the nasal prongs form a tight seal with the nares. Minimum supportive care includes frequent repositioning of the nasal prongs to ensure a seal. Finally, delivered pressure can leak through an open mouth, thereby failing to reach the lower airways. However, we typically find that infants in need of bubble CPAP often adjust and breathe with the device. They therefore receive the intended pressure support shortly after being fitted with the apparatus.

Given that severe respiratory distress can be associated with oropharyngeal dysphagia and aspiration, patients should not be fed orally while undergoing CPAP. Gastric feeds offer a reasonable alternative. The decision to place the gastric feeding tube nasally or orally should take into consideration the nasal CPAP seal on an individualized basis. We often find that an oral feeding tube in young infants works well. A less attractive alternative to gastric feeds is intravenous (IV) fluids. Infants can maintain hydration and adequate glucose levels with appropriate fluids and volume. However, IV fluids do not provide optimal calories for healing and growth. Infants who will be on nasal bubble CPAP for <72 h most often can be maintained with intravenous fluids, but those expected to require increased support for longer periods should have a gastric feeding plan.

Some infants, particularly those beyond the neonatal period, become agitated with bubble nasal CPAP. Sedation should be used with caution. Infants are particularly sensitive to sedation, and apnea is a significant problem in this population. Also, many resource-limited settings lack adequate staffing to safely monitor a sedated infant. If sedation is required, we suggest low-dose intermittent benzodiazepines. However, all other calming techniques should be exhausted first.

The clinical examination is the most important method for monitoring the efficacy of bubble nasal CPAP. We rely largely on the patient's respiratory rate, work of breathing, and lung examination. If available, pulse oximetry-measured cutaneous oxygen

saturation and capillary or arterial blood gases assays can add objective data, although they are by no means necessary for managing an infant on bubble nasal CPAP.

As the clinical status improves, there are many ways to wean the infant from bubble nasal CPAP. We often utilize sprinting trials where the infant is allowed progressively more frequent and longer intervals of time without support. This technique allows us to examine the patient off CPAP and gives the infant opportunities to regain strength. Prior to weaning from bubble CPAP, multiple factors should be considered, similar to weaning from any invasive or noninvasive respiratory support (Table 25.1). First, is the patient's disease process entering a convalescent phase, or is the patient likely to get worse before getting better? Second, has the patient's work of breathing improved with the additional support provided? We have found that weaning from bubble CPAP < 4 cmH_2O is not clinically useful. Therefore, we often move directly to traditional supplemental oxygen via a nasal cannula when a low level of support is reached or when the patient exhibits sustained decreased work of breathing, reduced respiratory rate, or improved mental status, suggesting clinical improvement. If the patient redevelops distress or persistent hypoxemia <90 % on less support, we place the patient back on CPAP of 5 cmH_2O pressure.

25.5 Facility Considerations

When deciding if a nasal bubble CPAP device is appropriate for a resource-limited hospital, we suggest the following considerations. First, are the minimum nursing human resources available to allow both a low nurse-to-patient ratio *and* 24-h coverage? Second, is there sufficient supplemental oxygen to operate a bubble CPAP device without compromising the availability of oxygen for less ill patients who may need supplemental oxygen *only*? Lastly, is the quality of clinical care for less critically ill patients optimized sufficiently enough to warrant addition of a more labor-intensive bubble CPAP device?

Conclusions

We have discussed the use of infant bubble CPAP in resource-limited settings. Supportive literature for this indication is sparse, and additional research is needed. The technology is widespread and effective in developed nations. As more practitioners implement and improve bubble CPAP in developing nation settings, clinical experience will continue to emerge.

Key Major Recommendations

- Respiratory disease primarily due to pneumonia is the leading cause of death in children under 5 years of age in resource-limited settings.
- Antibiotics and oxygen therapy are mainstays of treatment for severe respiratory disease. Many children may additionally benefit from noninvasive ventilation.

- A simple infant nasal bubble CPAP system can be built with limited and relatively inexpensive supplies.
- Attentive supportive care is a key component of successful bubble CPAP outcomes.
- Because high-flow supplemental oxygen used in the bubble CPAP circuit cannot be shared between patients, oxygen resources are a critical factor when determining the feasibility of using bubble CPAP in resource-constrained hospitals.

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Noninvasive Mechanical Ventilation During Neonatal Transport

26

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Keywords
Infants • Newborn • Neonatal transport • Noninvasive ventilation

26.1 Introduction

Approximately 1 % of newborn infants require neonatal transport for continuation of care [1–4]. Specialized neonatal transport teams are skilled in patient care, communication, and equipment management; and they are extensively trained in resuscitation, stabilization, and transport of critically ill infants [5–7]. Overall, 95 % of neonatal transports are by road, with air transport (helicopter or fixed-wing aircraft) accounting for only 5 % [3]. One-third of neonatal transports occur within the first 24 h after birth and the rest within the first week after birth [1–3].

There is limited information on the use of noninvasive mechanical ventilation (NIV) during neonatal transport of sick neonates [8]. Evidence comes from observational studies during land-based back-transfer of neonates receiving continuous positive airway pressure (CPAP) [9]. However, there are concerns of using NIV

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during retrieval altogether, with elective intubation and mechanical ventilation viewed as a safer option [10, 11]. Both the critically ill neonate and the neonatal transport team are exposed to mechanical stressors (e.g., shock, vibration, noise) during emergency transport, making clinical assessment almost impossible [12, 13]. In particular, endotracheal intubation is almost impossible during air transport because of vibration, limited space, and access to the infant's head [13].

26.2 Search Strategy

We reviewed books, resuscitation manuals, and articles from 1960 to the present with the search terms "infant," "newborn," "neonatal transport," "resuscitation," "airway management," "positive pressure respiration," "oropharyngeal airway," "laryngeal mask," "high-flow nasal cannula," "continuous positive airway pressure." We used the standard methods of the Cochrane Neonatal Review Group for inclusion, review, and quantitative methods.

26.3 Techniques

26.3.1 Oropharyngeal Airways

In 1907, Sir Fredrick Hewitt presented the first known artificial metal oral "air-way" after he recognized that upper airway obstruction was a common problem during general anesthesia [14]. In 1933, Arthur Guedel presented "the Guedel oropharyngeal airway," a black rubber modification of the metal airway [15]. It was designed to hold the tongue away from the back of the pharynx, thereby providing a clear channel for respired gases [16].

Oropharyngeal airways may be used to open the airway in floppy newborn infants or if mask ventilation is ineffective [17]. These airways come in traditional sizes of 000, 00, and 0 for preterm and term infants. Various surveys evaluating neonatal resuscitation practice reported that Guedel airways were part of the neonatal resuscitation equipment [18, 19]. However, the use of oropharyngeal airways during neonatal transport or resuscitation has not been systematically studied. Currently, there is one ongoing randomized trial comparing oropharyngeal airway during mask ventilation in preterm infants <34 weeks' gestation during neonatal resuscitation [20].

26.3.2 Low-Flow Nasal Cannulas

Low-flow nasal cannulas (LFNCs) are commonly used in both acute and chronic care settings to deliver oxygen [21]. Although, there is consensus that the nasal cannula is a low-flow device, disparities exist about the published

range of oxygen delivery at specific flow settings [21]. Wettstein et al. measured oxygen delivery by LFNCs at different gas flow rates [21]. The mean delivered oxygen ranged from 26 to 75 % at flow rates of 1–15 L/min [21]. In general, increasing the gas flow increased oxygen delivery. Interestingly subjects breathing with the mouth open had significantly higher oxygen delivery than those breathing with the mouth closed [21]. When using nasal cannulas, clinicians should be aware of device limitations affecting the delivery of expected oxygen concentrations.

26.3.3 High-Flow Nasal Cannulas

Binasal cannulas that deliver high gas flows (high-flow nasal cannulas, HFNCs) are becoming a popular form of respiratory support for preterm infants. HFNCs have also been proposed as an alternative to nasal CPAP in neonatal intensive care units to prevent extubation failure [21, 22]. A few small, nonrandomized studies have included infants being treated with HFNC for early or stable respiratory distress syndrome or for apnea of prematurity [22]. However, no study has reported HFNC use during neonatal transport. In summary, the use of HFNC as a primary therapy from birth requires further research.

Currently, two systems are available: (1) the Vapotherm system (Vapotherm, Stevensville, MD, USA) and (2) Nasal High Flow (NHF™) (Fisher & Paykel Healthcare, Auckland, New Zealand). Both devices deliver warmed, humidified high-flow (1–10 L/min) oxygen. A major concern with the use of HFNC is the variable descending airway pressure, depending on leaks at the mouth and the presence of nasal obstruction [22]. In comparison, airway pressure can be controlled with the use of CPAP [22]. Although several studies have reported their experience with HFNC devices [22], no randomized trial has compared the devices for efficacy or safety.

26.3.4 Nasal Continuous Positive Airway Pressure

Continuous positive airway pressure (CPAP) is a well-established therapy for managing respiratory distress in newborn infants. It is also an alternative to mechanical ventilation for most cases of less severe respiratory distress [23, 24].

Several case series have described the use of nasal CPAP during neonatal transport [8, 10, 11]. Simpson et al. reported their experience with six preterm infants at a median gestational age of 29 weeks and a median age at transfer of 23 days [11]. The transport had a median time of 45 min, and no problems were encountered during the transfers [11]. Bomont et al. reported their experience of 100 infants transported with nasal CPAP with predefined criteria [10]. The mean age of transport was 28 days. Overall, only 5 of the100 infants required intervention during transport. Four infants required stimulation because of apnea or bradycardia. One infant

required repositioning of the nasal CPAP prongs [10]. Resnick et al. retrospectively reviewed the use of nasal CPAP during neonatal transport in infants of >32 weeks gestation in Western Australia [8]. The use of nasal CPAP significantly increased from 33 % in 2002 to 59 % in 2004 in infants >32 weeks' gestation. Overall, 166 of 389 infants were transported on nasal CPAP, none of whom required intervention during transport [8].

Nasal CPAP during neonatal transport is feasible and appears safe. However, two of the studies described short-duration transport (mostly an hour or less). Only one study addressed long-distance transport [8, 10, 11]. Randomized studies comparing nasal CPAP and endotracheal intubation during short and long distances are necessary as are comparisons during land and air transport.

The reported case series used various nasal CPAP devices. Simpson et al. used the Infant Flow Driver (Electro Medical Equipment, Brighton, Sussex, UK) [11]. Bomont et al. relied on nasal CPAP delivered via a ventilator with which their staff was familiar [10]. Resnick et al. also delivered CPAP via a ventilator, using Hudson binasal prongs and the Stephan transport ventilator (F120 Reanimator; F. Stephan GmbH, Gackenbach, Germany) in CPAP mode [8]. Although several studies have reported their experience with CPAP devices, no randomized trial has compared those devices during neonatal transport.

26.3.5 Laryngeal Mask Airway

A laryngeal mask (LM) consists of an airway tube connected distally to a soft elliptical mask with an inflatable rim to fit over the laryngeal inlet. The proximal end connects to the ventilation device [25]. Size 1 LMs are recommended for all infants <5 kg as observational and randomized studies have demonstrated that the size 1 LM can be used in term and preterm infants >34 weeks or >2,000 g. In addition, one case of successful resuscitation of a premature infant with a birth weight of 800 g has been reported [26, 27].

Five cases of LM use during neonatal transport have been reported [28–30]. In four of these cases, inter-hospital transfer took place because of congenital airway malformation. In the fifth case, a newborn infant experienced sudden apneic episodes during helicopter transport [28–30]. All infants were successfully managed with a size 1 LM after either bag-and-mask ventilation or tracheal intubation had failed or had not been feasible [28–30]. In addition, no infant was given any sedatives or anesthetic drugs prior to LM insertion [28–30]. These cases demonstrate that an LM can be used during neonatal transport. Endotracheal intubation is almost impossible during air transport because of the vibrations, limited space, and access to the infant's head [13]. Hence, neonatal air transport services might consider the LM as part of their equipment. Randomized controlled trials are needed to compare endotracheal intubation versus use of the LM during neonatal transport before this practice can be advocated.

Key Major Recommendations

- Oropharyngeal airways have not been studied during neonatal transport and should therefore be used only in the clinical setting.
- Although the LFNC has not been reported during neonatal transport, it is a well-established therapy in the neonatal intensive care unit and can be recommended for neonatal transport.
- The HFNC has not been studied regarding neonatal transport and should be currently limited to clinical use.
- Nasal CPAP is a well-established respiratory therapy and can be used instead of intubation and mechanical ventilation in stable newborn infants requiring neonatal transport.
- Laryngeal mask usage has been described only in case reports. Randomized studies are urgently needed before LMs can be recommended for neonatal transport.

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Pathophysiology of Acute Respiratory Failure in Children with Bronchiolitis and Effect of CPAP

27

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Keywords
Noninvasive ventilation • CPAP • Children • RSV infection • Lower respiratory tract infection • High-flow cannula

27.1 Introduction

Acute bronchiolitis is the most common lower respiratory tract infection (LRTI) during the first year of life. Respiratory syncytial virus (RSV) infection is the most prevalent virus found in these children, accounting for 60–80 % of cases. The rate of hospitalization is less than 2 %. Up to 8 % of those hospitalized require ventilatory support [1, 2].

Three clinical presentations of severe bronchiolitis have been described. Acute hypercapnic respiratory distress is the most frequent form, resulting from respiratory muscle fatigue associated with alveolar hypoventilation. Recurrent severe apnea occurs in 1.2–23.8 % of cases [3, 4]. The latest clinical presentation is predominantly alveolar and can lead to acute respiratory distress syndrome (ARDS) [5]. Obstruction of the bronchioles increases the work of breathing (WOB), which represents the energy required to overcome the increased airway resistance. Infants, especially those born prematurely, are more prone to respiratory muscle fatigue.

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Prematurity, young age, and preexisting chronic respiratory and cardiac diseases are the main risk factors for severe bronchiolitis [1, 6]. When the WOB increases or persists for a long period, ventilatory support is required to prevent severe hypoxemia or hypercapnic coma.

Noninvasive ventilation (NIV) is most often delivered by continuous positive airway pressure (CPAP) via nasal prongs or mask. Some studies have reported the use of assisted spontaneous breathing (ASB) and biphasic positive airway pressure (BIPAP) as other NIV modalities [7–12]. High-flow cannulas (HFCs) deliver positive end-expiratory pressure (PEEP) that can attain 3 or 5 cmH_2O, and some studies suggested that it could obviate the need for endotracheal intubation [7, 8, 13–15]. There is no strong level of evidence that NIV avoids intubation and is beneficial for patients compared to intubation. During the last decade, however, increasing numbers of clinical and physiological studies have reported a good experience of NIV as the primary ventilatory support mode. Currently, CPAP is widely used as the first ventilatory support in many centers, with a decreasing rate of intubation.

The objective of this chapter is to summarize the impact of NIV techniques in the management of children with severe bronchiolitis requiring ventilatory support. Physiological knowledge is first discussed followed by clinical studies assessing the impact of NIV on the intubation rate and outcome. We then address the technical and practical aspects of NIV application in children according to age and clinical condition.

27.2 Physiological Aspects and Impact of NIV on Ventilatory Mechanics

In a physiological study of 37 infants, Hammer and colleagues showed that RSV infection could lead to two pulmonary function abnormalities [5]. The most common is bronchiolitis, an obstructive airway disease characterized by increased airway resistance (respiratory system resistance, R_{rs}), air trapping [high functional residual capacity/total lung capacity (FRC/TLC)], reduced TLC, and low respiratory system compliance (C_{rs}) compared with normal values. Typically, chest radiography of these children shows bilateral perihilar infiltrates and hyperinflation. Of the 37 infants, 10 had a resistive profile, corresponding to the criteria of acute respiratory distress syndrome (ARDS), with very low C_{rs} and R_{rs}. Radiography revealed bilateral alveolar consolidations. This form corresponded to RSV pneumonia.

The mechanism of apnea associated with RSV infection is not completely understood. Immaturity of central ventilatory centers is likely to be one of the explanations, which can explain the high prevalence of apnea in infants born prematurely and infants <2 months of age. The real incidence of apnea varies among studies, from 2.5 to 28.0 %, depending on the case mix. Among children admitted to the pediatric intensive care unit (PICU) the incidence is much higher [3]. It is probably important to distinguish primary apnea from apnea occurring after several hours of respiratory distress and a high level of WOB. The latter is likely to be due to muscle fatigue, which occurs more rapidly in young infants and those born prematurely.

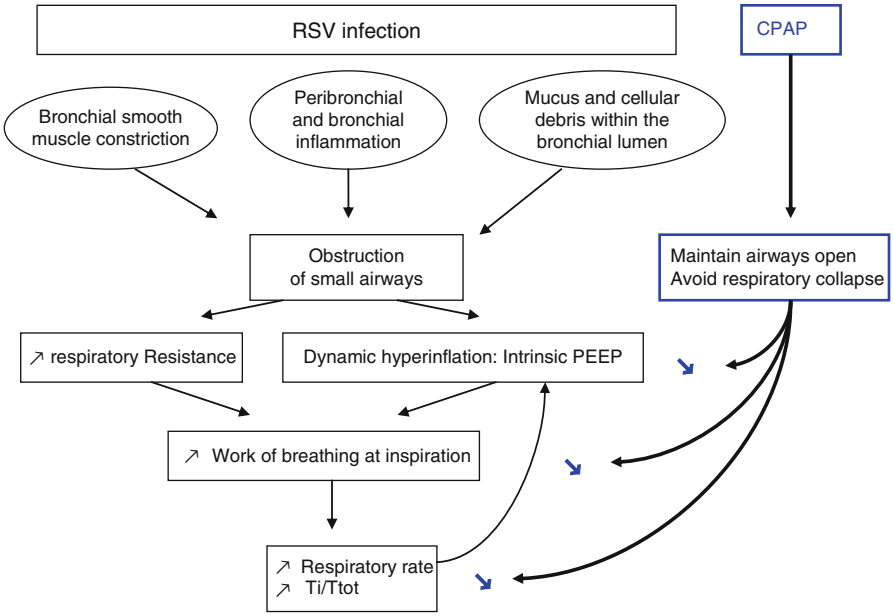

Fig. 27.1 Pathophysiology of the classic form of bronchiolitis: obstruction of small airways, its impact on ventilatory mechanics, and the effect of CPAP application. *CPAP* continuous positive airway pressure, *RSV* respiratory syncytial virus, *PEEP* positive end-expiratory pressure, *Ti* inspiratory time, *Ttot* length of a respiratory cycle

Obstruction of small airways is the main physiological phenomena of RSV infection in infants. It is the consequence of bronchial and peribronchial inflammation, plugging of airways by mucus and cellular debris, and bronchial smooth muscle constriction (Fig. 27.1). Consequently, the airway resistance and respiratory load increase. To preserve their pulmonary function, infants use their accessory respiratory muscles, increasing their WOB. They also increase their respiratory rate, but because of airway obstruction the duration of the expiratory period is too short to expire completely. Air is then trapped in the alveoli, generating dynamic hyperinflation and auto-PEEP. The inspiratory time/total respiratory time (T_i/T_{tot}) ratio increased as T_i decrease (Fig. 27.1).

Cambonie et al. from Montpellier and Essouri et al. from Paris have documented these respiratory changes and have shown that application of CPAP via nasal prongs led to a decrease in the respiratory rate (RR), T_i/T_{tot} ratio, and WOB assessed by esophageal and diaphragmatic pressure time products (PTP_{es} and PTP_{di}) (Fig. 27.1, Table 27.1) [7, 16, 17]. These measures were obtained using an esophageal and gastric probe with balloons. The PTP_{es} per breath was obtained by measuring the area under the diaphragmatic pressure (P_{di}) and the esophageal pressure (P_{es}) signal between the onset of inspiration and the end of inspiration. Essouri et al. showed in ten infants with severe bronchiolitis that the median level of auto-PEEP generated was 6.05 cmH_2O (range 3.9–9.2 cmH_2O) [16]. They showed that the decrease in

Table 27.1 Main physiological studies on the effects of CPAP on respiratory mechanics and on clinical parameters

						Main effects after CPAP					
Study	No.	Design	Age	Severity criteria	NIV type and setting	FiO_2	WOB	RR	pCO_2	Ti/Ttot	WCAS
Milési (2013) [17]	19	RCT	52,5	WCAS >4 RR 55 c/min pCO_2 56 mmHg	Nasal CPAP 6 cmH_2O Infant Flow	↘	↘	→	↘*	NA	↘
Cambonie (2008) [7]	12	Prospective No control	43	WCAS > 5 pCO_2 64 mmHg	Nasal CPAP 6 cmH_2O Infant Flow	↘	↘	→	↘	↘	↘
Essouri (2011) [16]	10	Prospective No control	45	RR 78 pCO_2 61.5 mmHg	Nasal CPAP 4-7-10 cmH_2O §	NA	↘	↘	↘	↘	NA

CPAP continuous positive airway pressure, *FiO_2* inspiratory fraction of oxygen, *RCT* randomized clinical trial, *RR* respiratory rate, *Ti* inspiratory time, *Ttot* total respiratory time, *WCAS* Wilson clinical asthma score

*The level of pCO2 decreased significantly from baseline in the group treated by CPAP 6 cm H_2O whereas the level did not decrease significantly in the control group

§ Three levels of CPAP were tested 4, 7 and 10 cm H_2O

WOB was greater with a CPAP level of 7 cmH_2O compared to 4 or 10 cmH_2O. This suggested that application of extrinsic PEEP decreased the pressure gradient between the mouth and alveoli at end-expiration. It allowed air to pass through the airways, reducing the work required for the next inspiration. The Montpellier team in France confirmed these results and the role of CPAP in a randomized controlled trial (RCT). They compared ten children treated with nasal CPAP at 6 cmH_2O to nine children managed with oxygen alone [17]. The T_i/T_{tot} and transcutaneous carbon dioxid partial pressure ($TcPCO_2$) were decreased in the CPAP group and the WOB was significantly reduced compared to that in control patients. This improvement of the WOB was correlated with the clinical improvement assessed by the modified Wilson Clinical Asthma Score (mWCAS).

27.2.1 Clinical Studies on NIV in Children with Severe Bronchiolitis

Beasley and Jones [18] and Soong et al. [19] were the first to report NIV use, especially CPAP, in infants with severe bronchiolitis. These preliminary studies showed that CPAP was able to decrease the $PaCO_2$ and RR of infants with severe bronchiolitis. Since 2004, numerous prospective or retrospective studies have been published and reported an increasing use of CPAP in this clinical setting (Table 27.2) [8–12, 17, 19–21]. However, there is no clear consensus on clinical use of CPAP compared to intubation and invasive ventilation [22].

27.2.1.1 Potential Advantages of NIV Techniques Compared to Invasive Ventilation

Complications of intubation and mechanical ventilation are well known. In infants, endotracheal intubation can be complicated by subglottic edema with a risk of evolution to tracheal stenosis. Mechanical ventilation of children with severe airway obstruction is challenging and may expose the airways and the lungs to high pressures or high volumes, causing lung injury. Most of infants who are mechanically ventilated require sedative drugs and sometimes muscle paralysis. The need for central venous access is common. These invasive procedures are associated with blood loss and expose children to nosocomial infection (e.g., pneumonia, urinary tract infection, bacteremia). The safety of sedative drugs in immature brains is not completely established. Hence, NIV represents a good alternative because its use rarely requires sedative drugs. On the other hand, the main risks of NIV are pneumonia aspiration in a child with an altered level of consciousness and potentially delayed intubation.

27.2.1.2 Clinical Effects of CPAP or NIV on Outcome

Most of studies have confirmed the results of early studies that CPAP and NIV improve gas exchange and the RR. Physiological studies suggested that application of CPAP improved gas exchange by decreasing the WOB and respiratory efforts, as assessed by the mWCAS.

Table 27.2 Clinical studies on non-invasive ventilation in children with severe bronchiolitis

Author (year)	Design	*N*	NIV mode	Interface	ETI avoided (%)	Clinical outcome	pH change	pCO_2 change	O_2 requirement	Infection	LOS, LMV	Major complication
Thia (2008) [21]	RCT cross-over	29	CPAP	Nasal prongs	–	–	–	↘	–	NA	NA	0
Milési (2013) [17]	RCT, physio	19	nCPAP, 6 cmH_2O	Nasal prongs	100	↘WOB ↘WCAS	NA	↘	↘	NA	NS	0
Cambonie (2008) [7]	Prospective, physio	12	nCPAP, 6 cmH_2O	Nasal prongs	100	↘ WOB ↘WCAS	NA	↘	↘	NA		0
Javouhey (2008) [10]	Retrospective, Pre/post	80 (15[a])	CPAP, BIPAP	Nasal prongs or mask	67		NA	NA	↘	↘[a]	ns	0
Larrar (2006) [11]	Prospective, NC	53	CPAP	Nasal prongs	75	↘RR		↘	NA	NA		0
Campion (2006) [8]	Prospective, NC	69	CPAP/BIPAP	Nasal prongs, facial mask	83	↘RR	↘	↘	NA	NA		0
Lazner (2012) [12]	Retrospective, NC	61	CPAP 4–6 cmH_2O Cuirass (P neg)	Nasal prongs or mask	90	↘RR	↘	↘	↘	↘ (compared to NR and IV)		0
Essouri (2011) [16]	Prospective, physio	10	CPAP (4-7-10 cmH_2O)	Nasal prongs	90	↘RR ↘WOB		↘				1 bacterial coinfection, NIV failure, IV
Ganu (2012) [9]	Retrospective 10 years	520 (285[a])	CPAP	Nasal or facial mask	83.2	NA	NA	NA	NA	NA	↘[b]	NA

LMV length of mechanical ventilation, *LOS* length of stay, *NA* not available, *NC* not controlled, *NIV* non-invasive ventilation, *NR* non responder, *physio* physiological, *RR* respiratory rate, *WCAS* Wilson clinical asthma score, *WOB* work of breathing

[a]The rate of ventilator-associated pneumonia was significantly decreased during the NIV period compared to the IV period

[b]Median LOS was reduced in children in whom NIV succeeded compared to those with IV and those who failed NIV

Few studies have compared this approach to the classic invasive ventilatory strategy on clinical outcome, such as the duration of ventilatory support, length of PICU stay, length of hospital stay (LOS), or ventilator-assisted pneumonia (VAP). Javouhey et al. in a pre/post study design showed that NIV as the primary ventilatory support was associated with a significant decrease in the intubation rate: from 89 to 52 % [10]. The NIV failure rate was 33 %. This approach was associated with a decreased incidence of VAP and a decrease in the number of children with oxygen requirement for >8 days [10].

Ganu et al. reported their 10-year experience of NIV for infants with severe bronchiolitis in their PICU from The Children's Hospital at Westmead in Sydney. Among the 520 infants admitted for bronchiolitis, 399 required ventilator assistance—285 with a trial of NIV, mainly CPAP [9]. They reported a significant increase in the use of NIV (2.8 % increase per year) along with a decline in the intubation rate (1.9 % per year). The percentages of infants failing NIV decreased over the study period, from 31.8 to 13.5 %. This decline was also observed in centers in which NIV was widely used as the primary mode of ventilatory support [9]. In our center, for example, this percentage decreased from 33 to 5 % during the 2011–2012 epidemics (personal data). The median hospital LOS was longer for infants who were intubated and invasively ventilated than for those in whom NIV succeeded. The hospital LOS was also significantly longer for children who failed NIV than for those with invasive ventilation. The same tendency had been found in a previous study [10]. Even with no control study, these results suggested that a strategy using NIV (mainly CPAP) as the primary ventilatory support was able to obviate the need for tracheal intubation.

27.2.1.3 Use of High-Flow Cannulas

More recently, a system of oxygen delivery was developed using heated and humidified high-flow gases delivered via nasal cannulas that can generate PEEP. The level of PEEP provided depends of the flow and the leaks but can reach 3–5 cmH_2O. This system has been used in children with severe bronchiolitis, with results similar to those achieved with CPAP, including improved alveolar ventilation and decreased RR, obviating the need for tracheal intubation [14, 15, 23] (Table 27.3). Physiological studies showed that high-flow cannulas (HFCs) are able to improve lung mechanics and ventilatory function by a washout of the nasopharyngeal dead space, a decrease in airflow resistance, and improved mucociliary clearance [24].

An RCT pilot study performed in 19 infants with moderately severe bronchiolitis showed that heated/humidified HFC therapy at 4–8 L/min improved the SpO_2 compared to a head-box oxygen group at 8 h (100 % vs. 96 %, $p=0.04$) and 12 h (99 % vs. 96 %, $p=0.04$) [13]. The stability of PEEP is not guaranteed and the level of PEEP reached can be insufficient to counterbalance the WOB. An in vitro study from Sivieri et al. showed that the airway pressure varied widely with the degree of nares occlusion by the prongs and by the amount of mouth leakage [25]. At 6 L/min HFC with the mouth open the airway pressure was <1.7 cmH_2O. It was <10.0 cmH_2O when the mouth was closed. Complete nares occlusion can generate high airway pressure (up to 20 cmH_2O) when the mouth is closed.

Table 27.3 Clinical studies on heated humidified high flow cannulas in children with severe bronchiolitis

Author (year)	Design	*n*	HFC set up	ETI avoided (%)	Clinical outcome	Ph change	pCO_2 change	LOS, LMV	Major complications
Schibler (2011)	Retrospective	167	8 L/min	96	4 % intubation Decrease intubation rate from 37 to 7 % 20 % decrease of HR and RR 90 min after HFC	NA	NA	2.33 (1.6–3.5)	0
McKiernan (2010)	Retrospective Pre/post study	115	7 L/min (infant cannula) or 8 L/min (pediatric cannula)	91	Decrease intubation rate from 23 to 9 %: 68 % reduction of intubation (adjusted for age, weight, and RSV status) Reduction of RR 1 h after initiation of HFC more important than without HFC	NA	NA	4 vs. 6 days	1 pneumothorax in each group Nasal, facial trauma
Abboud (2012)	Retrospective	113		81.4	Risk factors of failure: Low mean weight High pCO_2 before and after HFC Low RR before HFC High PRISM score				

ETI endotracheal intubation, *HFC* high flow cannula, *HR* heart rate, *NA* not available, *PRISM* pediatric risk of mortality, *RR* respiratory rate, *RSV* respiratory syncytial virus

Further studies comparing CPAP and HFCs would be useful to understand which children should benefit from CPAP rather than HFC. The latter system has the advantage of being simple to apply, usable in emergency units, and minimally expensive. Criteria used to initiate HFC or CPAP should be better defined and validated. A selection bias cannot completely be excluded because the level of severity of the infants treated is difficult to compare among studies. Moreover, as criteria to initiate ventilatory support are not well defined, those used in the various studies are likely to be different. Some authors have included children with severe respiratory distress and severe hypercapnic acidosis, whereas others have put children on ventilatory support considering only the signs of retraction or the level of tachypnea.

27.2.1.4 Criteria for Ventilator Support in Children with Severe Bronchiolitis

Criteria to initiate ventilatory support in children are not well defined and have not been validated. Most epidemiological studies have shown that infants with low weight and age < 42 days were more likely to be admitted to a PICU and ventilated. Other factors predisposing to mechanical ventilation were factors linked to a medical history of lung and cardiac diseases, prematurity, and/or neuromuscular disease [2, 9, 20].

Evans et al. analyzed criteria for CPAP requirement in a retrospective cohort of 163 patients admitted to their center for severe bronchiolitis [20]. Among these 163 children, 28 required CPAP. The authors found seven predictors for CPAP requirement: young age, low gestational age, low SpO_2, high level of oxygen requirement, respiratory and heart rates (RR, HR), and Glasgow Coma Score (GCS). Using receiver operator characteristic (ROC) curve analyses, they identified several thresholds: age < 11 weeks, SpO_2 < 95 %, RR > 54, HR > 163, and GCS < 15. The strongest predictor was a low SpO_2. The authors found a negative correlation between SpO_2 and O_2 requirement ($r = -0.656$), a positive correlation between age and weight ($r = 0.836$), and a positive correlation between gestational age and birth weight ($r = 0.824$). They did not find blood gas analyses as predictors of CPAP requirement [20]. Their results were limited by the retrospective nature of the study and by the small sample size.

Mansbach et al. identified factors associated with CPAP and/or intubation requirement in a prospective multicenter study that included 161 children [26]. In the multivariate analysis, factors associated with CPAP and/or intubation requirement were age < 2 months [odds ratio (OR) 4.3, 95 % confidence interval (CI) 1.7–11.5], maternal smoking during pregnancy (OR 1.4, 95 % CI 1.1–1.9), birth weight < 5 lb (OR 1.7, 95 % CI 1.0–2.6), breathing difficulty began <1 day before admission (OR 1.6, 95 % CI 1.2–2.1), severe retractions (OR 11.1, 95 % CI 2.4–33.0), and room air SpO_2 < 85 % (OR 3.3, 95 % CI 2.0–4.8) [26]. Identifying patients at high risk of CPAP requirement is important because it can help the physician's decision about transferring the patient to the unit able to initiate the ventilatory support required.

Curiously, blood gas analyses have not been found to be good indicators of ventilatory support requirement except in the study of Campion et al., where a high

Table 27.4 Criteria of ventilatory support selected by investigators in the French prospective multicenter study (at least two criteria are needed)

Criterion 1	Respiratory rate	RR > 70/min for age< 6 month RR > 60/min for age ≥ 6 month
Criterion 2	Oxygenation	SpO_2 < 92 % whatever the level of O_2 requirement
Criterion 3	Respiratory acidosis	pH < 7.3 and pCO_2 > 70 mmHg
Criterion 4	Apnea	Apnea with SpO_2 < 90 % and/or bradycardia < 90 if age < 6 month or < 80 for older
Criterion 5	Neurological signs	Hypotonic and drowsiness in the absence of stimulation

RR respiratory rate, *SpO_2* percutaneous oxygen saturation

Table 27.5 Absolute criteria of intubation (one criterion is sufficient) defined a priori by investigators of the French multicenter study

Criterion 1	Respiratory arrest	Inability to maintain efficient ventilation with SPO_2 > 90 % after 2 min of bag–mask ventilation
Criterion 2	Refractory hypoxia	Inability to maintain SpO_2 > 90 % during 1 h
Criterion 3	Neurological failure	Altered level of consciousness with low reactivity or agitation not responding to oxygenation

level of CO_2 before CPAP was predictive of NIV failure defined as the need for invasive ventilation [8]. Similarly, composite scores of respiratory distress failed to identify the group of patients requiring ventilator support. In two French studies, high PRISM scores were predictors of the need for invasive ventilation. However, as this score is calculated 24 h after admission, it cannot help the physician make clinical decisions [8, 11].

The criteria for initiating CPAP should differ from those used to initiate invasive ventilation. Unfortunately, no reported studies have made such a comparison of these criteria. Therefore, the ventilatory strategy for children admitted with severe bronchiolitis is based on little evidence. CPAP and HFC can be proposed as first-line ventilatory support in most cases, although HFC is probably insufficient in children with severe hypercapnic acidosis. Response to this first line of ventilatory support must be assessed within the first 2 h following its initiation. Nonresponders are at high risk of complications and often require invasive ventilation. NIV in BiPAP or ASB mode or in pressure control mode can be attempted provided that rapid assessment is done and strict supervision is observed.

For better selection of patients who will respond to CPAP, some studies have assessed risk factors of NIV failure. Most of these studies were retrospective and compared patients whose ventilatory support was NIV alone versus those who were intubated after an NIV trial [8, 10, 20, 27–29]. Failure was defined as the need for intubation. Most of these studies included children with all types of respiratory distress, not bronchiolitis alone. The level of FiO_2, ARDS and a high level of FiO_2 (over 80 %) 1h after starting NIV were found as factors associated with NIV failure in children with severe respiratory distress of various causes [27, 28]. Larrar et al. identified the absence of a reduction in PCO_2 as a predictive factor of NIV failure in a CPAP study. Abboud et al., in an HFC study, came to the same conclusion [11, 23].

A French prospective multicenter study noted that a minimal reduction in CO_2 and a low increase in pH measured 2 or 4 h after NIV initiation were strong predictors of NIV failure [30]. In that study, the various centers had defined criteria for ventilatory support and absolute criteria for invasive ventilation (Tables 27.4 and 27.5). The results suggested that early assessment of the response to NIV is crucial.

27.3 Practical Aspects of NIV Use and Risk Factors of Failure

Noninvasive ventilatory supports include a number of systems that deliver pressure support to the patient via an interface. The CPAP delivery system has to be reliable, with good stability of the pressure during all the respiratory cycle length. It also has to be easy to use and install in children. Interfaces are chosen according to their ability to be connected to the CPAP delivery systems while minimizing air leaks, dead space, and discomfort.

27.3.1 High-Flow Cannulas

To deliver heated/humidified oxygen, an air-oxygen flow generator is required combined with a heated humidifier. The circuit tubing and the size of the cannula differ according the age of the child. For infants weighing <10 kg, small-volume circuit tubing is required. Infant or pediatric cannulas can be used. Adult circuit tubing and cannulas are used for children weighing ≥10 kg.

27.3.2 Systems for Delivering CPAP

As children with severe bronchiolitis requiring ventilatory support are young (<42 days) and of low weight, CPAP systems developed for neonates are used, such as Infant Flow (EME, Electro Medical Equipment, Brighton, UK), Infant Star 950 (Nellcor Puritan Bennett, San Diego, CA, USA), and Bubble CPAP (Fisher and Paykel Healthcare, Auckland, NZ). In the latter system, a water column delivers PEEP. In PICUs, an ICU ventilator or CPAP machine may be preferred. No study has compared the stability of PEEP in these delivery systems. It is well known that PEEP stability can be affect by the level of leaks, the degree of mouth opening, and the level of airflow in the circuit.

The choice of the interface is crucial. The ideal interface is one that is easy to install, minimizes leaks, and does not cause skin or mucosal injury.

27.3.2.1 Nasal Prongs

Low-resistance nasal prongs or cannulas are the interfaces most frequently used in infants with bronchiolitis. The nasal approach is preferred because infants predominantly breathe through the nose. In infants with bronchiolitis, the tolerance is reportedly good, although no study has specifically addressed skin or mucosal injuries in the context of bronchiolitis. As nasal breathing has to be preserved, nasal

obstruction, which frequently occurs during RSV infection, should be systematically treated and monitored. Nasal obstruction is a source of discomfort and agitation for children treated by nasal CPAP. Consequently, nasal lavage with NaCl 0.9 % every 3 or 4 h is recommended. The choice of the cannula's size is important to limit leaks and avoid nose injuries. It is recommended that nasal prongs of different sizes with different inter-nostril distances be readily available. To limit mouth leaks, a dummy is frequently used and sometimes a chinstrap is required. To avoid skin irritation or ulceration and to improve the patient's comfort, colloid ulcer dressings (e.g., Comfeel, Coloplast) are applied to protect the nasal bridge as well as the nostrils. In our experience, nasal prongs or cannulas are well tolerated by infants weighing up to 5 kg. For larger infants, nasal masks are often better tolerated.

27.3.2.2 Small, Nonleaking Masks for Neonates

During the last decade, manufacturers have designed small nasal masks specifically intended not to leak. They allow us to put small infants on CPAP with standard ventilators in the PICU. These masks are also available for the Bubble CPAP system and the Infant Flow CPAP generators. It is also possible to use a nasal mask with intentional leakage to connect infants to a CPAP or BiPAP machine. The Resmed Sullivan Infant Bubble mask (ResMed, Waterloo, Australia) is used for the smallest infants and the Small Child Profil Lite mask (Philips Respironics, Murrysville, PA, USA) for the others. Skin protection can be used to minimize skin irritation. The choice of the headgear or bonnet fitted to the head's form and size is important to avoid mask displacement, which can increase leaks, and fastening the mask too tightly on the face, which could increase the risk of skin injuries.

27.3.2.3 Bucconasal Masks, Facial Masks, Helmets

Bucconasal masks are used only when the leaks are interfering with synchronization of the infant with the ventilator for NIV. When the mouth is open or if the nose is obstructed, application of nasal CPAP becomes ineffective. A major concern is the absence of specific bucconasal masks for infants. Most often, anesthesia masks or adult nasal masks are used. However, in these cases, the risk of skin injury is much higher than with nasal masks, particularly laceration or ulceration of the nasal bridge. Skin protection with colloid dressings must be used to prevent these injuries. Progress in the design of bucconasal masks is needed to enable NIV in infants and young children. Helmets represent an alternative in children weighing >5 kg. They cannot be used in smaller children because the helmet compresses the chest, reducing its efficacy. Some experiences with helmets have been reported even in small children. They report rather good tolerance and improvement of alveolar ventilation [31, 32].

27.4 Ventilator Settings: Level of CPAP

Essouri and colleagues showed that a CPAP level of 7 cmH_2O was better than either 4 or 10 cmH_2O in 10 children admitted to a PICU for severe bronchiolitis [16]. The decrease WOB, assessed by PTP_{di} and PTP_{es}, was more significant with 7 cmH_2O.

This level was closest to the auto-PEEP level (6.3 cmH_2O) and is consistent with the level of CPAP used in the main clinical studies (Table 27.2). Based on these results, starting with a level between 6 and 8 cmH_2O is recommended.

For HFC, the recommended flow by the manufacturer is 1–2 L/kg/min. In a retrospective study, Schibler et al. used a fixed flow of 8 L/min but did not explain the reason for this choice [15]. In practice, we start with a flow of 1 L/kg/min and increase it to 2 L/kg/min according to the tolerance of the child. As already noted, the optimal level of flow is unknown and depends of the degree of nares obstruction and mouth leakage.

Concerning the BiPAP or ASB ventilation modes, as no study has been performed comparing different ventilatory settings we are not able to make any recommendations. The studies that have reported the use of BiPAP or ASB in patients with bronchiolitis used a level of PEEP varying from 4 to 8 cmH_2O and inspiratory pressures between 10 and 20 cmH_2O. The level of pressure support varied from 4 to 12 cmH_2O. NIV pressures >20 cmH_2O are associated with a high risk of gastric dilatation by gas. To minimize this phenomenon, a nasogastric tube is routinely inserted to deflate the stomach when necessary. In our clinical practice, when an infant is switched from CPAP to NIV on pressure support, we start with a level of PEEP equal to the level of CPAP used and then add pressure support of 6 cmH_2O above PEEP or an inspiratory pressure of 6 plus PEEP. Then, after assessing the efficacy and tolerance, we adapt the ventilator setting or the interface, avoiding exceeding 20 cmH_2O. The inspiratory pressure is titrated by 2 cmH_2O increments to a level where the RR, signs of WOB, and blood gases are improved.

The main problem with NIV in pressure support mode, such as BiPAP, is asynchrony. The sensitivity of ventilatory triggers is sometimes insufficient for young infants, who are unable to trigger a ventilatory cycle. On the contrary, when the sensitivity of the trigger is too high, and when the leaks are important, autotriggering may appear, generating discomfort and asynchrony. Control of leakage is another factor contributing to synchrony: If the ventilator is unable to compensate for the leaks, the inspiratory time can be prolonged into the period when the child wants to expire. These causes of asynchrony are a source of discomfort and poor tolerance of NIV in infants.

No study has been performed comparing different ventilatory modes with different ventilators in infants who suffer from severe bronchiolitis. Neurally adjusted ventilatory assistance (NAVA) is a promising mode that would limit the incidence of asynchrony. Liet and colleagues reported three cases of infants with severe bronchiolitis treated with this mode during invasive mechanical ventilation and showed that NAVA was able to improve synchrony, decrease the oxygen requirement, and decrease peak airway pressure from 28 ± 3 to 15 ± 5 cmH_2O [33].

It has been shown In 15 neonates and children that NAVA decreased patient–ventilator asynchrony and the peak inspiratory pressure [34]. The percentage of time in asynchrony was lower in the NAVA group (8.8 %) than in the pressure (33.4 %) and flow (30.8 %) trigger groups (ventilated either in pressure control or pressure regulated volume controlled). Moreover, the peak inspiratory pressure was 1.9–2.0 cmH_2O lower in NAVA than in the pressure and flow groups, respectively ($p<0.05$ for both) [34].

We reported our experience of NAVA in NIV mode in 18 infants with severe bronchiolitis. The tolerance and the feasibility were good, and 16 of 18 infants had NAVA mode success, thereby avoiding invasive ventilation (personal communication). As no study comparing classic NIV to NAVA NIV has been reported, this technique cannot be recommended but represents a new mode to be considered when asynchrony is detected frequently with classic NIV.

27.5 Discussion

During the last decade, ventilatory support for children with severe bronchiolitis has radically changed. Nasal CPAP is become the first mode of NIV for children who meet the criteria for ventilatory support. Numerous studies have suggested that this strategy is associated with a decreased need for intubation and invasive ventilation. Although the level of evidence of improved outcomes related to this strategy is low, in the absence of prospective controlled studies the data published have shown that children can be safely managed less invasively without prolonging the PICU stay. Some studies suggested that responders to nasal CPAP had a lower length of PICU stay than those who were intubated.

Physiological studies have provided some evidence that a CPAP level of 6–7 cmH_2O is able to decrease the WOB and improve alveolar ventilation in children with obstructive bronchiolitis [7, 16, 17]. The application of extrinsic PEEP to the airways at a level greater than the level of auto-PEEP generated by dynamic obstruction of small airways allowed reduction of efforts made by the child to initiate the next inspiratory cycle. This mechanism is responsible for the clinical improvement observed in the children after initiation of nasal CPAP. The responders are those whose RRs are reduced and CO_2 levels and heart rates are decreased within 2–4 h of starting NIV with CPAP. Early identification of those who will respond is crucial so as not to delay applying NIV with two levels of pressure or intubation with invasive ventilation.

More recently, the HFC, which is able to deliver humidified/heated oxygen, has been reported to be another alternative to nasal CPAP [14, 15, 23]. This system has been shown to generate a low level of PEEP, induce washout of nasopharyngeal dead space, match inspiratory flow rates in infants, and improve mucociliary clearance [24]. Children with apnea and those with severe hypercapnic acidosis are more likely to fail HFC and can be treated by nasal CPAP. As no study has been conducted comparing HFC to nasal CPAP, no recommendation can be drawn. There is a crucial need of studies to better distinguish groups of children who will respond to HFC, to CPAP, or to NIV because the level of expertise and equipment differ significantly between these modes. HFC can be initiated in the emergency or intermediate care units, whereas CPAP and NIV should be reserved for use in an intermediate care unit or an ICU according the level of the teams' experience. Stratification of respiratory distress severity is required for better patient selection at admission. We know that patients with a medical history of chronic lung, heart, or neuromuscular diseases are at higher risk of complications and failure of HFC or CPAP. Young

infants, particularly those born prematurely and those with low weight, are more likely to require ventilatory support [1, 6]. However, the clinical score, biological markers, and blood gas criteria associated with ventilatory support and with CPAP failure, are not well defined and require further study. Moreover, as no study has been performed on NIV at two pressure levels in bronchiolitis, there is no evidence that NIV after CPAP or HFC failure can obviate the need for intubation and invasive ventilation. Only a multicenter prospective study comparing different ventilatory strategies would be able to determine the best ventilatory support treatment.

Technically, manufacturers have improved their products to facilitate CPAP application. Nasal masks and nasal prongs of different sizes are now available, allowing us to fit the equipment to the child's facial and head morphology. The objectives of these interfaces are to facilitate setup, limit the dead space, and reduce air leaks. Experience and the use of specific nursing protocols are factors associated with a high success rate of NIV techniques, suggesting that only teams with a high level of training and experience should apply NIV.

Key Major Recommendations

- Nasal CPAP and HFCs are the best first option for ventilatory support of children with severe bronchiolitis. Their use may avoid intubation and invasive mechanical ventilation.
- There is an insufficient level of evidence of the efficacy of NIV on mortality or morbidity criteria.
- NIV with pressure support is an option when CPAP fails.
- Early assessment (within the first 2 h) of responders to CPAP or HFC is required to prevent secondary critical deterioration.
- Improved blood gas levels after CPAP is a good indicator of response to CPAP.
- Infection, apnea, and young age are associated with NIV failure.
- Nasal cannulas are the most appropriate interface for infants weighing <5 kg.
- The optimal CPAP level to prevent muscle fatigue is probably around 7 cmH_2O.

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Noninvasive Mechanical Ventilation in Pediatric Practice

28

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Keywords
Noninvasive ventilation • Pediatric • Acute respiratory failure

28.1 Introduction

Noninvasive ventilation (NIV) use in pediatrics is now rapidly gaining acceptance. It refers to a technique that increases alveolar ventilation by supplying a transpulmonary pressure gradient through an oronasal or nasal mask. Avoiding any indwelling artificial airways, such as endotracheal or tracheostomy tubes, and their complications constitutes its main advantage.

Infant respiration is predominantly dependent on diaphragmatic function. NIV helps decrease the work of breathing by unloading the diaphragm. NIV also stabilizes the highly pliable chest wall and reduces retractions in young infants. Apnea and hypopnea frequency decrease by maintaining upper airway patency. NIV increases oxygenation and carbon dioxide washout by alveolar recruitment and improves cardiac output by decreasing left ventricular afterload [1, 2].

28.2 Indications for NIV

There are no well-defined clinical conditions for which NIV can be considered as standard therapy in the pediatric population. Standard NIV therapy protocols do not exist for high-risk pediatric infections. NIV should be initiated based on the

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presence of dyspnea or tachypnea (respiratory rate > 75th percentile according to age), hypoxemia, or respiratory acidosis [2]. Favorable experiences in pediatric use of NIV are limited to cystic fibrosis, pneumonia, status asthmaticus, acute chest syndrome, pulmonary edema, postextubation acute respiratory failure (ARF), acute exacerbation of chronic respiratory failure, and hypoxemic ARF [1, 3]. NIV application seems to decrease the need for intubation in immunocompromised patients [4]. The most promising application of NIV in pediatrics is the treatment of respiratory failure in patients with neuromuscular disease and restrictive chest wall deformities [1]. NIV has a favorable influence on respiratory tract infections in children with neuromuscular disorders [5]. NIV combined with heliox have also been described as effective in infants with severe bronchiolitis [2]. Furthermore, tracheotomy weaning in children can be achieved with NIV support [6]. NIV was a preferred method for treating pediatric respiratory failure during the influenza (H1N1) pandemic in 2009, but the small numbers of patients do not let us to execute a protocol different from other NIV applications. None of the reports from various geographical parts of the world mentioned any additional risks due to NIV in H1N1-infected pediatric patients [7–12].

There are practically no data on how to initiate NIV in children. Face masks are appropriate for older children, but they are not routinely used in infants because of the difficulty obtaining an adequate fit and seal. Oronasal masks help minimize air leaks and improve performance in critically ill children, but they may cause anxiety in infants. Short binasal prongs and nasal masks seem to be the preferred means of delivering NIV to infants. The helmet is an alternative interface with potential advantages of better tolerability, less air leakage, avoided facial skin irritation, stable fixation, and preserved ability to speak and cough. Helmets can be applied regardless of the facial contour, which is a grave problem for fixation in children [1, 2, 13].

Noninvasive ventilation can be administered in either the intensive care unit (ICU) or at home. An initial anxiety may be reduced by reassuring the child, providing parental presence, and initiating therapy with a low pressure setting, gradually increasing it over time. Despite this titration process to avoid discomfort from high gas flow, some children require sedation to improve cooperation and synchronization. Midazolam or ketamine can be used to prevent ineffective inspiratory efforts and double-triggering, which are the most common types of asynchrony. Ketamine has an added advantage in patients with asthma and acute bronchospasm because of its bronchodilatory effects. The triggering function should be set as sensitive as possible while avoiding auto-triggering. Leak compensation software should be used if available [1, 2]. To start with an inspiratory maximal airway pressure of 6–8 cmH_2O, increasing up to 16 cmH_2O if needed is reasonable. Expiratory (continuous) pressure may be set at 3–5 cmH_2O and increased up to 10 cmH_2O [1]. An appropriate rise time should be selected according to the patient's comfort. An initial FiO_2 of 0.4–0.6 is the preferred setting to keep the SO_2 at 95 %. The child should be encouraged to hold the mask and be invited to breathe through it or the helmet for a few seconds before connecting it to the ventilator, thereby achieving good adaptation. Air leaks and straps should be checked periodically and a humidifier added to the circuit [2].

28.3 Discussion

When tracheal intubation is required, it should not be delayed as delay might worsen the prognosis. For this reason, children treated with NIV should be placed on cardiac and respiratory monitors and continuous pulse oximetry applied. Continuous evaluation of the respiratory rate, heart rate, pH, oxygen saturation, and clinical performance should be used as a guide for modifying respiratory assistance parameters. In addition, radiologic assessment may be informative regarding the prognosis. Nevertheless, only two parameters, the mean airway pressure (MAP) and FiO_2, were shown to have a potential to discriminate the success and failure with NIV. MAP represents the effects of all pressure parameters. MAP > 11.5 cmH_2O and $FiO_2 > 0.6$ cmH_2O predicts failure in 80–90 % of patients [3]. A decrease in the respiratory rate is a fairly reliable sign of an effective response to NIV. Other signs of a positive response to NIV are improved oxygenation, decreased retractions and accessory muscle use, and a reduction in the number of airway occlusion events in patients with upper airway obstruction. In case of continued respiratory distress, poor oxygenation, excessive secretions, or hemodynamic instability, endotracheal intubation should immediately be performed [1]. Apnea and pneumonia are the two independent risk factors for NIV failure [14].

Noninvasive ventilation application mainly causes interface-related minor complications in children. Potential adverse effects of nasal interfaces include nasal bridge pain, ulceration, mucosal dryness, and gastric insufflation. Relatively common complications include skin irritation at the interface margin and eye irritation. Major complications are rare but include tension pneumothorax, depressed cardiac output, and progressive hypercarbia. Patient–ventilator asynchrony is the major disadvantage [1–3].

Contraindications to pediatric NIV application are life-threatening hypoxemia, obstruction of the upper airways, vomiting, impaired mental status with cough or gag reflex loss causing inability to protect the airway, intractable apneic episodes, facial surgery, burns or trauma, congenital facial or airway abnormalities, recent upper airway or upper gastrointestinal tract surgery or bleeding, poor cooperation or inability to tolerate the mask, inability to handle oral secretions, hemodynamic instability or cardiac arrhythmia, and cyanotic congenital heart disease. NIV should not be started in the presence of exhaustion with paradoxical abdominal and thoracic motion, $PaO_2:FiO_2 < 150$ mmHg and $PaCO_2 > 55$ mmHg, or pHa < 7.30 [1, 2].

Key Major Recommendations

- Factors essential to NIV success include the timing of the intervention, close monitoring, use of comfortable and well-fitting interface devices, and appropriate selection criteria for patients.
- Patience, skill, experience, and motivation of the care team in addition to coaching and encouraging the patients are also closely linked to NIV success.

- It has been commonly suggested that if improvement is not seen soon after implementation, endotracheal intubation for conventional MV should be implemented without delay.
- More prospective studies are required to clarify the candidates who can potentially benefit from NIV.

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29 Noninvasive Mechanical Ventilation in Patients with High-Risk Infections and Mass Casualties in Acute Respiratory Failure: Pediatric Perspective

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Keywords
Noninvasive ventilation • Children • Acute respiratory failure • Pandemic • Influenza

29.1 Introduction

Respiratory problems are common symptoms in children and common reason for visits to the pediatric emergency department (PED) and admission to the pediatric intensive care unit (PICU). Although the great majority of cases are benign and self-limited, requiring no intervention, some patients need respiratory support. Invasive mechanical ventilation (IMV) is a critical intervention in many cases of acute respiratory failure (ARF), but there are absolute risks associated with endotracheal intubation (ETI). On the other hand, noninvasive ventilation (NIV) is an extremely valuable alternative to IMV. A major reason for the increasing use of NIV has been the desire to avoid the complications of IMV. It is generally much safer than IMV and has been shown to decrease resource utilization. Its use also avoids the complications and side effects associated with ETI, including upper airway trauma, laryngeal swelling, postextubation vocal cord dysfunction, nosocomial infections, and ventilator-associated pneumonia. There are a number of advantages

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of NIV including leaving the upper airway intact, preserving the natural defense mechanisms of the upper airways, decreasing the need for sedation, maintaining the ability to talk while undergoing NIV, and reducing the length of hospitalization and its associated costs [1–3].

Noninvasive ventilation in the pediatric population with ARF as a therapeutic tool has become an option in recent years and is being applied increasingly. It can be initiated wherever the patient presents with ARF—in the PED, PICU, or other areas of the hospital. Over the last decade, several studies have suggested successful application of NIV in patients with ARF. Although numerous controlled studies and meta-analyses have shown its efficiency in different forms of ARF (e.g., exacerbation of chronic obstructive pulmonary disease and acute cardiogenic pulmonary edema in adults), the evidence supporting its using in infants and children with ARF is still limited, and there are no generally accepted guidelines for its use. However, the most recent physiological and randomized studies indicate that the early application of NIV improves the breathing pattern and gas exchange and reduces respiratory muscle effort in children [1–7].

Today, NIV is considered a first-line intervention for various causes of ARF and may be considered in the context of pandemics such as H1N1 or severe acute respiratory syndrome (SARS). In these circumstances, most of the studies showed that the use of NIV decreased the rate of ventilator-associated pneumonia and reduced the duration of oxygen requirement without prolonging the hospital stay [4–8]. On the other hand, there is controversy about the possibility that NIV increases the spread of viral infections during pandemics. Moreover, since the outbreak of SARS in 2003, pandemic planners around the world have classified NIV as a high risk procedure that should be used cautiously because of possible spread of the infection [9]. Similarly, Ontario's Provincial Infectious Diseases Advisory Committee in Canada recommended that NIV be avoided for patients with febrile respiratory illness during the 2009 influenza pandemic (H1N1) [10]. Additionally, the World Health Organization's interim guidelines on the prevention and control of acute respiratory diseases associated with health care have included NIV among the aerosol-generating procedures in which there is possibly an increased risk of respiratory pathogen transmission [11]. However, there has been no evidence-based information to support the claim that the use of NIV increases the risk of transmitting infectious diseases.

29.2 Analysis

The use of NIV for children with ARF caused by viral infections and experiences using NIV in these children are increasing worldwide. In the literature, most of the studies related to using NIV in the case of ARF have been done during pandemics. Also, there is still a large variety of practices and a paucity of published data in pediatrics. Nonetheless, after the most important two viral pandemics during the last decade, especially the last one with influenza A(H1N1), most of the societies

including above-mentioned and the European Respiratory Society, European Society of Intensive Care Medicine, and The American Association for Respiratory Care have recommended that NIV not be used to treat ARF due to H1N1, particularly in severely ill patients. Thus, NIV is accepted as a high-risk procedure that should be used cautiously because of possible spread of infection [9–15].

During the last decade, we experienced two viral pandemics that ultimately spread worldwide. One was occasioned by severe acute respiratory syndrome (SARS), which is an emerging infectious disease that first manifested in humans in China in 2002. In an observational study of the SARS outbreak that included adult patients from China, the effectiveness of NIV in the treatment of ARF was investigated. It was shown that NIV was effective in preventing the use of endotracheal intubation in 70 % of patients because of its early initiation in the SARS patients. In this study, none of the health workers, including doctors, nurses, and health-care assistants, acquired SARS from the patients. As an explanation, NIV was applied in a negative-pressure environment with strict personal protection and close monitoring of the health status of all involved staff [4]. In another study from Toronto during SARS, the use of NIV was discouraged especially after clinicians contracted the disease when a patient was intubated following NIV failure [9]. Therefore, some clinicians considered NIV contraindicated for ARF due to airborne respiratory diseases unless it is used in a negative-pressure isolation room and strict precautions are taken [4, 9].

The second viral pandemic was influenza A(H1N1) in 2009. The role of NIV in children with ARF due to influenza A(H1N1) was also the subject of controversy, although NIV has become an important mechanism for ventilator support for pediatric ARF. Severe respiratory failure is a well-recognized complication of pandemic H1N1 influenza infection. Rello et al. [16] applied NIV to a small number of critically ill patients with pandemic H1N1 infection complicated by ARF. Most of these patients subsequently required IMV support. Therefore, NIV is generally not recommended for patients with the novel influenza infection complicated by pneumonia and ARDS. NIV temporarily improves oxygenation and reduces the work of breathing but does not necessarily alter the course of the disease. The need for NIV is an indication of severe disease and likelihood of IMV. In addition, hemodynamic instability and multi-organ failure are contraindications for applying NIV [2, 16, 17].

In a multicenter study from India that included adult patients with infected influenza A(H1N1) during the outbreak of influenza A(H1N1) in 2009, patients requiring invasive ventilation at admission had a higher mortality rate than those managed with NIV and those not requiring ventilation. NIV was considered based on guidelines regarding ARF that included severe dyspnea at rest [respiration rate (RR) > 35/min], $PaO_2/FiO_2 < 200$ while breathing oxygen through a mask, and use of accessory muscles of respiration or paradoxical abdominal motion. Criteria for a response to NIV, or lack of it, were RR improvement, the Glasgow Coma Score (GCS), and blood gases improvement. Intubation was considered if there was intolerance to the mask or there was a contraindication to continued use, including nasal bridge

necrosis, persistent hypoxemia not responding to appropriate and tolerated levels of positive end-expiratory pressure (PEEP), or persistent or worsening respiratory acidosis. In all, 32.1 % of patients were managed with NIV. However 17 % of all patients failed NIV and were intubated and ventilated invasively. Patients who could be started on and managed with NIV had significantly better survival compared with those who required IMV at the onset. The need for invasive ventilation at admission was found to be associated with a higher mortality rate [18].

In another multicenter observational study, Nicolini et al. [19] showed that NIV was effective in preventing endotracheal intubation in 48 % of the patients with ARF and pulmonary infiltrates due to an H1N1 infection. Moreover, NIV success was found to be associated with a lower incidence of "new" infectious complications and increased ICU survival compared to those patients who failed NIV. Additionally, a high Simplified Acute Physiology Score (SAPS II) and a low PaO_2/FiO_2 are related to high risk of intubation and mortality. Therefore, they emphasized that the timing of NIV application is crucial in determining its success [19].

In a multi-center study investigating the outcome of critically ill children with H1N1 in PICUs from Turkey, NIV was applied 7.2 % of all patients. Two of them survived (3.4 %) and four did not (16.0 %). In the same study, mortality rates were found to be higher in patients with H1N1 infection and conventional mechanical ventilation. However, multi-organ failure and high mortality and organ dysfunction scores were associated with increased mortality. The nonsurvivor group required conventional mechanical ventilation, high-frequency oscillatory ventilation, renal replacement therapies, inotropes, and vasoactive treatment. However, this study is not enough to discuss NIV efficiency because NIV was applied in a small number of patients and high mortality rates were found [20].

Torres et al. [7] described the clinical characteristics and outcome of children admitted to the PICU with influenza A(H1N1) from Argentina during the 2009 pandemic. NIV was applied to 13.3 % of all patients (19/142) and the success rate was 63 % with no deaths. Twelve of these patients recovered from NIV without mechanical ventilation. Although there was a high rate of mortality (47 %) in their study, all of the children who received NIV survived. Age < 24 months, mechanical ventilation, use of inotropes, respiratory co-infections, and a history of asthma were found as predictors of mortality [7]. The use of NIV versus conventional ventilation was addressed in another randomized trial that included a selected small group of hypoxemic patients. According to the results, serious infections secondary to intubation developed more frequently in the conventional ventilation group. The duration of ventilation and the ICU stay were shorter in the NIV group [1].

Another controversial aspect of NIV application is whether NIV should be used in patients with acute respiratory distress syndrome (ARDS) due to pneumonia or other causes. According to a consensus in Spain, NIV cannot be considered a technique of choice in adult patients with ARDS, although it may be useful in experienced centers and in cases of ARF. Within this consensus, the failure rate of NIV in

patients with ARF secondary to ARDS due to influenza virus A(H1N1) infection was 75 %, the mortality rate among the patients in which NIV failed was 38 %, and delays in starting intubation were associated to an increase mortality risk. The general recommendation was that early intubation of patients with evidence of NIV failure should be instituted for better results [21].

There is also controversy about the use of NIV in children with ARDS. There are only two studies in children with ARDS, and they encourage the use of NIV. Essouri et al. [6], in a descriptive study, recommended that NIV be used as the first line intervention in children with severe ARF due to community-acquired pneumonia or respiratory failure in immunocompromised patients, although the failure rate in their study was 78 % among patients with ARDS. Munoz-Bonet et al. [5] reported an NIV success rate of 81 % regarding control of ARF due to pneumonia, thereby avoiding tracheal intubation and its complications. Two parameters were associated with NIV failure, including MAP > 11.5 cmH_2O and the FiO_2 (0.6). On the other hand, the NIV success rate was 50 % in patients with ARDS. Therefore, the authors thought that the diagnosis of ARDS should not be a contraindication for the use of NIV, especially in immunosuppressed patients because it prevents tracheal intubation They also recommended that NIV be applied as early as possible.

Fowler et al. [22] investigated the risk of contracting SARS among physicians and nurses who cared for patients with SARS during the epidemic. They showed that the nurses and physicians who directly participated in endotracheal intubation had a dramatically increased risk of developing SARS. Similarly, nurses caring for patients undergoing NIV may have been more likely to develop SARS than nurses caring for patients with SARS treated with conventional ventilation. The difference, however, was not statistically significant. Their study indicated that tracheal suctioning was one of the certain high-risk components of SARS nursing care, but it was not generally performed in patients with SARS ventilated with NIV. Therefore, endotracheal suction might be considered not to increase the risk of respiratory droplet dispersion.

During the SARS outbreak, SARS working groups developed guidelines for procedures, including endotracheal intubation, cardiopulmonary resuscitation, and mechanical ventilation. These guidelines specify that the use of personal protection devices is mandatory, the most qualified individual available should perform the endotracheal intubation, and procedures such as prolonged NIV and aerosolized bronchodilator or humidification therapies generally should not be initiated where safe alternatives are available. At that time, many clinicians seeing patients during the Asian SARS outbreak thought that NIV was preferred over early endotracheal intubation and mechanical ventilation because of the risk to HCWs involved with endotracheal intubation [21–24].

Influenza viruses are thought to be spread by droplets, but the role of aerosol dissemination is unclear. Droplets in the respirable range (~5 μm) may play a significant part in transmission, but the role of aerosols has been questioned.

There are few studies that have quantified the viral load in droplets or aerosols. A subgroup of patients, often with underlying chronic disorders or risk factors such as immunosuppression, can develop pneumonia/respiratory insufficiency with H1N1 swine flu or other influenzal infection and require treatment by oxygen therapy, nebulized medication, and ventilatory support. These therapies are thought to generate droplets or aerosols. Based on pandemic experience, gas leakage via exhalation ports may also disperse infectious particles into the environment. During pandemics, HCWs and other patients are at risk for contamination because of the virus. In addition, pandemic planners have highlighted the potential need for providing mechanical ventilation in environments that are safe for HCWs. They have recommended airborne precautions for HCWs who are managing patients with pandemic influenza with increased transmissibility and during procedures that may generate small aerosol particles of respiratory secretions. However, it is not known how exhaled air and particles may disperse during NIV in clinical settings. There is no reliable marker that can be safely introduced to the patients [23–25].

Previous studies have not assessed droplet or aerosol generation during respiratory support interventions in clinical practice. Hui et al. [24] assessed the risks of single-circuit NIV in spreading infectious particles through the bleeding port and orofacial mask interface using a high-fidelity human patient simulator. They showed that substantial exposure to exhaled air occurred within 0.5 m from patients receiving NIV, and higher ventilator pressures result in a wider distribution of exhaled air (Fig. 29.1). Therefore, they recommended that HCWs be aware of the potential risks of viral transmission during NIV and take strict contact and droplet precautions, wearing full personal protective equipment.

An observational study of influenza A and influenza B in exhaled breath also showed viral RNA in one-third of infected patients, and 99 % of particles had a diameter of <5 μm when sampled during tidal breathing [25]. Generally, NIV and chest physiotherapy are accepted as droplet-generating procedures, producing droplets of >10 μm. Because of their large mass, most fall on local surfaces within 1 m. Therefore, HCWs providing NIV and chest physiotherapy working within 1 m of an infected patient should have a higher level of respiratory protection. Infection control measures designed to limit aerosol spread, such as negative-pressure rooms, may have less relevance. The results of these studies may have infection control implications for other airborne infections, such as SARS and tuberculosis, as well as for pandemic influenza infection [10, 22, 25].

Simonds et al. [23] showed the characteristics of droplet/aerosol dispersion around delivery systems during NIV treatment by measuring droplet size, geographical distribution of droplets over time after the interventions were discontinued, and the impact of modification of the NIV circuit in clinical practice. They found that NIV using a vented mask produced large droplets (>10 μm) from patients and coryzal subjects compared with baseline values. This increase in large droplets was not seen using the NIV circuit modification. Preliminary analysis suggests that droplet size falls to within a baseline range within 20–40 min of discontinuing NIV [23].

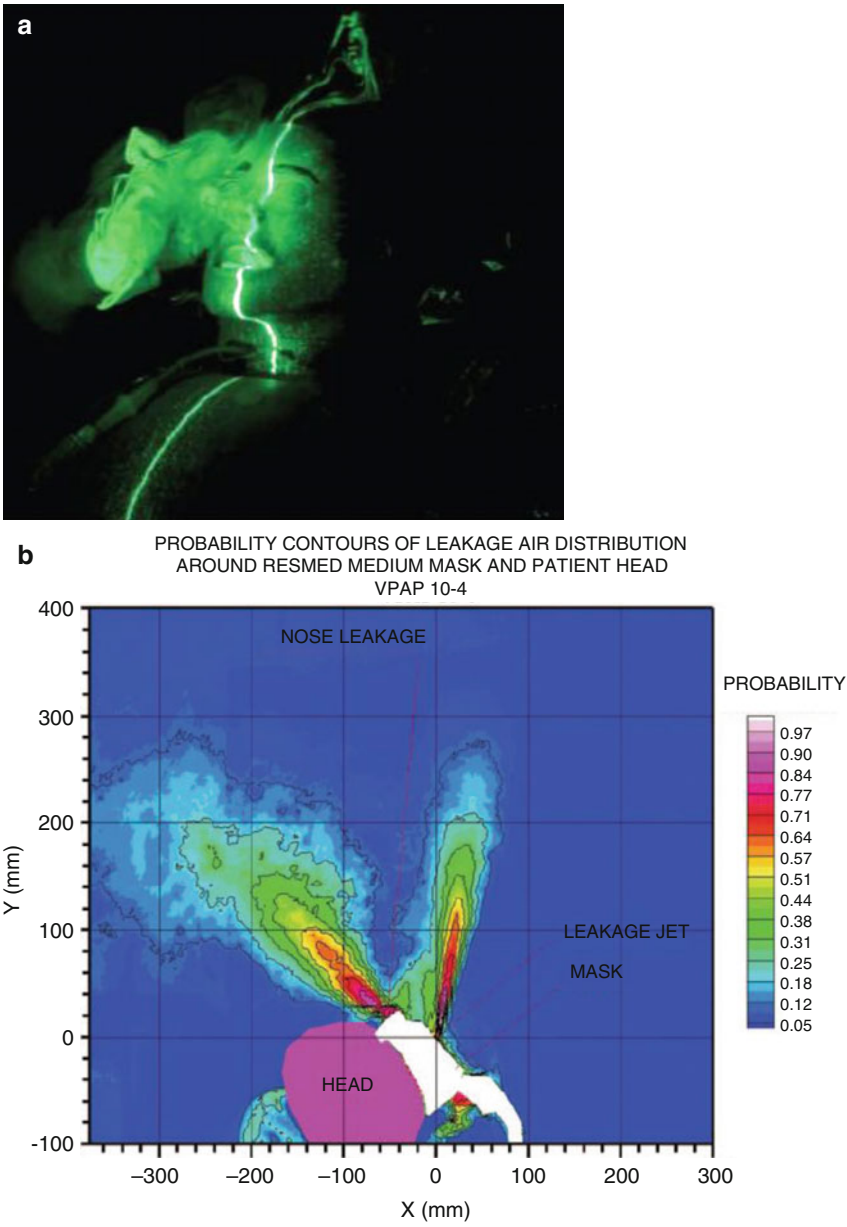

Fig. 29.1 (**a**) Airflow leakage around a mask is shown by a laser light sheet. Visualization of airflow around the oronasal mask was facilitated by marking the air with smoke particles produced by an M-6000 smoke generator (model N19; DS Electronics, Tempe, AZ). The laser light sheet illuminated the smoke particles after the mask airflow leakage. (**b**) Inspiratory/expiratory positive airway pressures (IPAP 10 cmH_2O/EPAP 4 cmH_2O) with leakage from the nasal bridge (sagittal plane). There is a <10 % probability of exposure if the health care worker (HCW) stands outside the light blue contour regions. If the HCW is standing outside a radial distance of approximately 0.25 m from the mask, there is <10 % chance of exposure to the exhaled air. (**c**) Note that the highest probability of encountering the patient's exhaled air is not directly above the mask in the sagittal plane but to the side, where a HCW may typically stand (From Hui et al. [24])

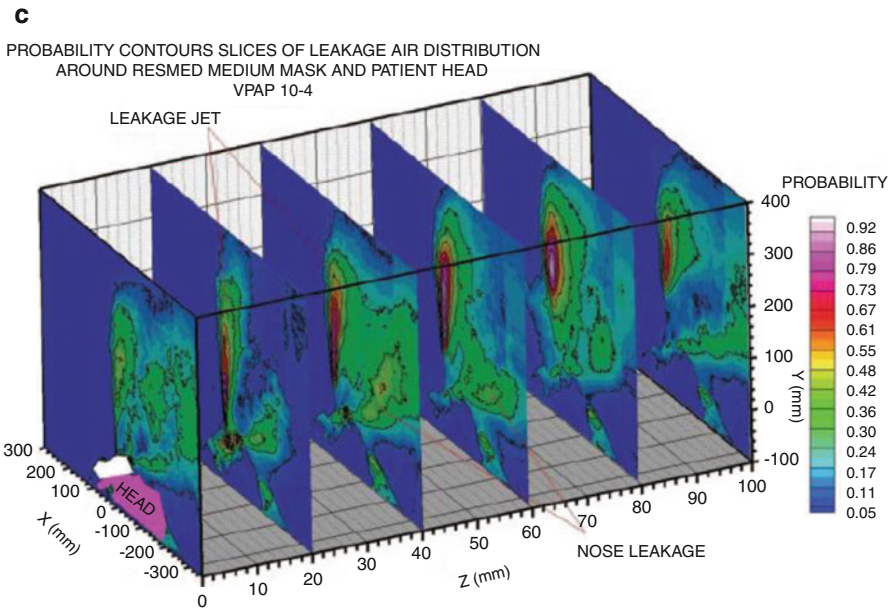

Fig. 29.1 (continued)

29.3 Discussion

Noninvasive ventilation is an effective treatment modality for patients with ARF due to pneumonia or acute cardiogenic pulmonary edema and for immunocompromised patients, both adults and children, with pneumonia and postextubation respiratory failure. It is also known that NIV can markedly reduce the need for endotracheal intubation and the rate of complications. It shortens the hospital length of stay and improves survival. NIV can be used to decrease a patient's dyspnea and work of breathing and improve gas exchange. Therefore, patients with hypercapnic forms of ARF are most likely to benefit from NIV. However, clinicians should not forget that NIV is a complementary technique and cannot replace endotracheal intubation under all conditions.

The success of NIV relies on several factors, including the type and severity of ARF, very low arterial blood pH, marked alteration in mental status, underlying disease, location of treatment, and the experience of the team. The time factor is also important. To prevent further deterioration, early NIV must become an important part of the first-line treatment of ARF. In addition, the success of invasive ventilation is dependent on various clinical aspects and the organisation of care—but also on a number of technical issues. These technical points are the ventilator interface, type of humidifier, and ventilator used and its capabilities for triggering and pressurization. The general care of the NIV patient is different from that for a patient

undergoing invasive ventilation and potentially has a great influence on the success of the technique.

Noninvasive ventilation has become an important mechanism for ventilator support in children with ARF. However, if the ARF is due to the influenza A(H1N1) virus, NIV has become controversial. Future prospective randomized controlled studies should help determine, with more methodology, the physiological effects of NIV and the most appropriate group of patients potentially able to benefit from this promising technique during a pandemic. The studies have shown that in critically ill children with confirmed or probable H1N1 viral infection and severe ARDS the use of NIV can result in significant improvement in oxygenation. It may improve the mortality rate for this very high-risk population.

We believe that NIV is a promising alternate to standard therapies in the treatment of ARF in pediatric patients. In our experience, patients placed on NIV should be monitored closely and the mode of ventilation reviewed if there is a lack of response within a few hours after starting therapy. Treatment of early ARDS associated with respiratory viral infections—e.g., influenza A(H1N1)—using NIV could also be tried after identifying patients who require endotracheal intubation in negative-pressure rooms under strict precautions. Because of the high demand for critical care beds during a pandemic, NIV may have a role in reducing the estimated ICU load as it can be applied anywhere in the hospital.

In conclusion, the efficiency of NIV in children with ARF depends on the degree of hypoxia, the underlying disease, and illness severity scores. NIV can even be used in immunosuppressed patients, although cautiously, because intubation is a strong predictor of mortality and nosocomial infections. The success rate of NIV depends on early application, the experience of the institution, and the team's familiarity with the technique.

Key Major Recommendations

- Noninvasive ventilation can be regarded as an option of choice in children with ARF and ARDS due to respiratory viral infections in centers with a large experience and under conditions of strict personal protection.
- Initiating procedures that may be associated with increased dispersal of respiratory droplets—as in patients with SARS or influenza A(H1N1)—must be conducted with caution. There may be risks that require many forms of support. Decisions must be made on an individual patient basis with due attention to the hazards for both patients and HCWs.
- The outcome of NIV in patients with ARF due to acute lung injury, ARDS, or pneumonia depends on the degree of hypoxia, the presence of co-morbidities and complications, and the illness severity score. In these circumstances, NIV should be cautiously considered early and not delay needed intubation.

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Part IV

Prognosis and Risk Factors

Factors Involved in Aerosol Transmission of Infection and Control of Ventilation in Healthcare

30

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Keywords

Aerosol transmission of infection • Air droplets • Droplet nuclei • Infectious aerosol dose • Healthcare worker • Aerosol-generating procedures • Human simulator patient

30.1 Introduction

Experience with the recent viral pandemics has generated a renewed interest in the study of the transmission modes of respiratory pathogens. It not only provides better understanding of the pathogenesis of the disease but also of the rational design of infectious-control strategies. Hospital-acquired infections still account for many hospitalizations and deaths around the world, with many of these infections being transmitted via aerosolized microorganisms to patients and healthcare workers (HCWs).

The generation of such infectious aerosols of human respiratory pathogens can occur via three modes of transmission, which are not mutually exclusive: aerosol transmission, transmission by large droplets, and self-inoculation of the nasal mucosa by contaminated hands. The aerosol mode is arguably the most important because of its impact on hospital infection control, safety of the HCWs requiring specialized isolation rooms, personalized protective equipment, and caution with certain procedures.

Growing evidence supports that from the classic early studies by Wells regarding air borne transmission and spread of diseases in the hospital environment and its HCWs [1]. Many of these infections can be prevented. In this chapter, we discuss

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the biological and mechanical factors involved in the transmission of respiratory pathogens and their consequences. Chapter 31 discusses preventive measures to decrease airborne transmission of infections.

30.2 Definitions

- Airborne transmission: passage of microorganisms from a source to a person through aerosols, resulting in infection of the person with or without consequent disease.
- Aerosols: solid or liquid particles suspended in the air. The size of the particles (0.001 to >100 μm) allows them to remain airborne for a variable amount of time. Infectious aerosols contain pathogens.
- Short-range airborne infection route: transmission between an infected source and the susceptible host within a short distance, generally <1 m.
- Long-range airborne infection route: transmission of infected particles carried from the source for a long distance to the susceptible host by airflow (within rooms, between rooms, distant locations), generally >1 m.

30.3 Factors Involved in Aerosol Transmission

30.3.1 Mechanics of Aerosol Transmission

When studying bio-aerosols generated by humans, it is important to distinguish between the initial particle diameter and the final diameter after evaporation of water in ambient air. These "droplet nuclei" are involved in the long-range transmission route but can also cause infection in the short range.

Once infectious droplets are released, the main factors that determine how they are transported are their size, type (with or without structural lipids), airflow patterns, humidity, and temperature. Humidity alters the evaporation rate of the droplets and therefore affects droplets' size. Knight estimated the time taken for particles to fall to the floor in a 3-m height room. Particles of 1–3 μm in diameter remain suspended almost indefinitely, 10–μm droplets stay in the air 17 min, 20-μm droplets remain for 4 min, and 100-μm droplets fall to the ground after 10 s [2]. The droplet size thus affects how airflow patterns distribute their deposition. Temperature changes also greatly influence the exchange flows between rooms. Both temperature and humidity affect the lipid envelope and protein coat, affecting the period of survival. Temperatures above about 24 °C appear universally to decrease airborne bacterial survival. Transport of such airborne droplets is driven by various other environmental factors, such as the local ventilation airflow (windows, doors, ventilation systems), the movement of people and their clothing, and thermal and airflow gradients produced by various pieces of equipment.

Another important consideration for the pathogenesis of aerosolized transmitted infectious diseases is the penetration and deposition of these infected particles in the respiratory tract. Particles >20 μm rarely penetrate below the trachea, particles 5–10 μm have 50 % penetration of the tracheobronchial tree, and particles <5 μm have

less penetration of the alveolar region (30 %) [3]. Receptors are required for some infectious agents to initiate successful infection and eventually disease. Whereas bacteria and fungi can exist independently of host cells, viruses require specific receptors to which they can bind before entering and replicating within particular host cells. This requirement has been offered as one of the explanations for why certain individuals were infected with avian influenza A (H5N1) and perhaps why others were not. Differing receptor distribution patterns in the upper and lower respiratory tracts among individuals can affect the ease with which inhaled airborne viruses can cause infection and disease [4, 5]. Finally, the nature of the infecting agent and the human respiratory activity itself may cause a different variety of organism to be expelled with differing effects on secondary cases. The physiology of a cough suggests that it is more likely to bring up and expel deep-seated organisms from the lower respiratory tract (e.g., influenza, *Staphylococcus* and *Streptococcus* bacterial species)than the sneeze or normal speech, both of which are more likely to expel organisms inhabiting the upper respiratory tract(e.g., rhinoviruses and coronaviruses).

30.3.2 Aerosol Infectious Dose

The infectious risk of transmission is critically affected by parameters such as the pathogenicity of the infectious agent, its infectious dose, rate of biological decay, and environmental interaction of the infectious agent (Table 30.1) [6, 7]. The infectious dose varies among individual pathogens and their hosts. Not only are immunocompromised hosts more susceptible to infection, even with low infectious doses they become more effective source spreaders because the pathogen is poorly controlled, leading to super-spreading events. Knowledge of the infectious dose can help estimate the number of air changes required in an indoor environment to reduce the pathogen concentration to a safe level.

Some organisms resist environmental degradation better than others. *Mycobacterium tuberculosis* has a thick cell wall and can survive for long periods in various environments. Nonlipid enveloped viruses (rhinovirus, adenovirus) survive longer in high relative humidity (RH), whereas lipid-enveloped viruses influenza, coronavirus, measles, varicella zoster virus (VZV)] survive longer in low relative humidity. Minimal survival for both lipid and nonlipid membrane viruses occurs at intermediate RH (40–70 %) [7]. Data on human corona virus 229E indicate a half-life of 3 h at 80 % RH, 67 h at 50 % RH, and 27 h at 30 % RH, suggesting that if confronted with a coronavirus epidemic the room RH should be kept high (≥80 %) [8]. Influenza survives on nonporous surfaces for 24–48 h; 8–12 h on cloth, paper, or tissues; and 5 min on hands. It also has been shown that the severe acute respiratory syndrome–coronavirus (SARS-CoV) and the influenza virus can remain infectious in alkaline stool and respiratory specimens, respectively, up to 4–7 days at room air temperature.

30.3.3 Source of Infectious Agents

Infectious aerosols can be generated in many ways and in many settings. The infectious patient is the main source of aerosolized particles. During normal exhalation

Table 30.1 Diseases and pathogen characteristics associated with aerosol infectious transmission [6, 7]

	Aerosol route				Temperature	Relative humidity
Disease/pathogen	Direct contact	Large/medium droplet aerosol	Droplet nuclei	Basic reproductive number(R0)[a]	Viability and infectivity	
Chickenpox/ shingles (varicella zoster)	Yes	Yes	Yes	10–12	Decreased by higher temperature	Stable at low (20–30 %) RH
Coronavirus (SARS-CoV)	Yes	Yes	Yes	2–3	Decreased by higher temperature	Stable at low (20–30 %) RH
Gram-negative bacteria	Yes	Yes	No	N/A	Decreased by higher temperature	Lower at intermediate/high (50–90 %) RH except *Klebsiella* and *Pasteurella*
Influenza	Yes	Yes	Yes	1.68–20	Decreased by higher temperature	Stable at low (20–30 %) RH
Legionellosis (*L. pneumoniae*)	No	Yes	No	N/A	Decreased by higher temperature	Stable at > 65 % RH
Measles	Yes	Yes	Yes	15–17	Decreased by higher temperature	Stable at low (20–30 %) RH
Meningitis					Decreased by higher temperature	Lower at intermediate (50–70 %) RH
N. meningitidis	Yes	Yes	No	1.2–1.36		
H. influenza	Yes	Yes	No	N/A		
S. pneumoniae	Yes	Yes	No	1.4		
Whooping cough (*B. pertussis*)	Yes	Yes	Yes	15–17	Decreased by higher temperature	N/A
Pneumonia					Decreased by higher temperature	Lower at intermediate (50–70 %) RH
S. pneumoniae	Yes	Yes	No	1.4		
M. pneumoniae	Yes	Yes	No	N/A		
C. pneumoniae	Yes	Yes	No	N/A		

Common cold					Decreased by higher temperature	Stable at high (70–90 %) RH
Rhinovirus	Yes	Yes	No	N/A		
RSV	Yes	Yes	No	1.2–7.1		
Staphylococcal disease	Yes	Yes	No	N/A	Decreased by higher temperature	Lower at intermediate (50–70 %) RH
Tuberculosis	No	No	Yes	1–10	Decreased by higher temperature	N/A
Fungi	No	Yes	Yes	N/A	Increased by higher temperature	Increased by higher RH

RH relative humidity, *N/A* not available or quantified, *RSV* respiratory syncytial virus

[a]R0 = the number of secondary cases arising from a single index case in an otherwise totally susceptible population

breathing, with individual heterogeneity, droplets can project up to 1 m in room air, whereas sneezing can project droplets several meters. Normal exhalation produces particles ≤1 μm, explained by the fact that aerosol particles are generated in the lower respiratory tract, where larger particles tend to be retained via impaction or deposition. A sneeze can generate up to 40,000 droplets 0.5–12.0 μm in diameter [9]. A cough can generate about 3,000 droplet nuclei—the same as talking for 5 min. More than 65 and 40 % of the droplets produced by talking and coughing, respectively, are <75 μm [10, 11].

30.3.4 Aerosol-Generating Procedures

Many aerosol-generating procedures (AGPs) are known to stimulate cough and promote generation of aerosols. The risk of infectious transmission is unclear, however, because of scarce scientific evidence to demonstrate the creation of aerosol-associated infections with these procedures, the burden of potential viable microbes within the created aerosols, and the mechanism of transmission to the host.

Several simulation studies with different AGPs have been published that tried to compensate for the lack of knowledge concerning airborne transmission with these procedures. Hui et al. studied aerosol particle production from various AGPs—oxygen mask, jet nebulizer, and noninvasive ventilation (NIV)—using a human patient simulator (HPS)and measurement of smoke particles. The aerosol particles exhaled using oxygen masks with flow at 4 L and 12 breaths per minute were captured by digital images showing that the exhaled air reached peak distances of 0.40 m [12]. The maximum dispersion distance of smoke particles through the nebulizer side vent was 0.45 m lateral to the HPS at normal lung condition but increased to 0.54 m in the presence of mild lung injury and beyond 0.8 m in the presence of severe lung injury [13]. Exhaled dispersion was also studied during NIV in the HPS simulating mild lung injury in an isolation room with negative pressure using different masks and increasing inspiratory positive airway pressure (IPAP) (10–18 cmH_2O) and stable expiratory positive airway pressure (EPAP) (4 cmH_2O). Using a ResMed Ultra Mirage mask, the dispersion was 0.40 m at an IPAP of 10 cmH_2O and only increased to 0.45 m with an IPAP of 18cmH_2O [14]. The distance dispersion using the Respironics Image 3 mask, which requires an additional exhalation device to avoid CO_2 retention, was 0.65 m with 10 cmH_2O of IPAP and increased to beyond 0.95 m with an IPAP of 18cmH_2O. With the Respironics Comfort Full 2 mask, the distance was 0.65 m with IPAP at10–14 cmH_2O and increased to 0.85 m with IPAP at 18 cmH_2O [15]. These studies used human simulator models or normal subjects mimicking respiratory distress, but the HPS may not closely reflect the behavior of sick patients. Also, the smoke particles measured were considerably smaller (<1 μm) than droplets generated by coughing and sneezing (5 to >10 μm). Therefore, the behavior of smoke particles may not accurately represent droplet dispersion.

Simonds et al. [16] evaluated the characteristics of droplet/aerosol dispersion around delivery systems during NIV, 60 % O_2, nebulizer treatment, and chest physiotherapy by measuring the droplet sizes at <20 cm from the face or mask and at 1 m

distance. They also assessed the decay of droplets over time after discontinuing an intervention and the impact of modifying the NIV circuit by inserting a viral/bacterial filter in clinical practice. Three groups were studied: normal control subjects ($n=12$); subjects with coryzal symptoms ($n=11$); adult patients with chronic obstructive pulmonary disease (COPD) admitted because of an infective exacerbation ($n=21$). NIV using a vented mask without the filtered circuit and chest physiotherapy are droplet-, not aerosol-, generating procedures. They created droplets >10 μm in the COPD ($p=0.042$) and coryzal ($p=0.044$) patients but not in normal controls. Because of their large mass, most of the droplets landed on local surfaces within 1 m. O_2 did not increase droplet count in any size range. The only device that produced an aerosol was the nebulizer, consistent with nebulizer characteristics. (Nebulizers do not disseminate large droplets from patients.) These findings suggest that HCWs providing NIV and chest physiotherapy working within 1 m of an infected patient should have a high level of respiratory protection. Control measures designed to limit aerosol spread, such as negative-pressure rooms, may have less relevance.

Tran et al. [17] published a systematic review of AGP and the risk of transmission of acute respiratory infections to HCWs. They identified only ten studies of very low grade evidence by the Grading of Recommendations Assessment, Development and Evaluation(GRADE) evaluation (five relevant case–control studies and five retrospective cohort studies, with no relevant systematic reviews, meta-analyses, or randomized controlled trials identified) in China, Singapore, and Canada during the SARS outbreak. Procedures reported to present an increased risk of transmission in HCWs exposed versus nonexposed workers included pooled odds ratios (OR) with 95 % confidence intervals (CI): for tracheal intubation, OR 6.6; noninvasive ventilation, OR 3.1; tracheotomy, OR 4.2; manual ventilation before intubation, OR 2.8. Other intubation-associated procedures, endotracheal aspiration, suction of body fluids, bronchoscopy, nebulizer treatment, high-flow O_2 administration, manipulation of O_2 mask, or bilevel positive air pressure/continuous positive air pressure (BIPAP/CPAP) mask, defibrillation, chest compression, insertion of a nasogastric tube, and collection of sputum were not associated with aerosol transmission. The studies evaluated only the risk of transmission of SARS–CoV and may not be generalizable to other acute respiratory pathogens. In addition, it is difficult to identify the specific part of a given procedure, which may be complex and involve several maneuvers that impart the greatest risk of transmission.

Key Major Recommendations

- Generation of infectious aerosols of human respiratory pathogens can occur by aerosol transmission, transmission by large droplets, and self-inoculation of the nasal mucosa by contaminated hands.
- Main factors that determine how infectious droplets are transported are their size, type (with or without structural lipids), airflow patterns, humidity, temperature, local ventilation airflows, and thermal and airflow gradients.

- The risk of transmitting infection is critically affected by parameters such as the pathogenicity of the infectious agent, the dose, the rate of biological decay, and environmental interaction of the infectious agent including the host's immune status.
- Aerosol-generating procedures associated with an increased risk of transmission to HCWs include tracheal intubation, NIV, tracheotomy, and manual ventilation before intubation.
- Endotracheal aspiration, suction of body fluids, bronchoscopy, nebulizer treatment, high-flow O_2 administration, manipulation of the O_2 mask or the BiPAP/CPAP mask, defibrillation, chest compressions, insertion of a nasogastric tube, and collection of sputum are not associated with aerosol transmission

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Noninvasive Mechanical Ventilation to Prevent Intensive Care Unit-Acquired Infection

31

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Keywords
Noninvasive mechanical ventilation • ICU • Nosocomial infection

31.1 Introduction

Although invasive mechanical ventilation (IMV) is an effective technique for supporting alveolar ventilation, it has many associated complications. In intensive care unit (ICU) patients, nosocomial infections are major causes of mortality and morbitidy. The use of invasive devices such as the endotracheal tube is the most important factor for producing nosocomial infections [1]. Ventilator-associated pneumonia (VAP)—defined as the development of parenchymal lung infection after at least 48 h of IMV—is the most common nosocomial infection in the ICU. It is associated with prolonged hospitalization, increased health care costs, and mortality. The incidence of VAP ranges from 6 to 52 %. The risk increases at a rate of 1–3 % for each day that a patient is on IMV. The main pathogenic mechanism for the development of VAP is aspiration of colonized oropharyngeal secretions at the time of intubation or throughout the period on IMV. The risk factors for VAP are shown in Table 31.1.

Noninvasive mechanical ventilation (NIMV) is the delivery of mechanical ventilation using techniques that do not require an endotracheal airway. In recent years, it has been successfully used in selected populations as an effective treatment for acute respiratory failure (ARF). During the last decade, randomized controlled trials have shown that the addition of NIMV to standard medical treatment of patients with ARF improves vital signs and gas exchange, avoids the need for intubation, and reduces complications and mortality. Selection of appropriate patients is crucial

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Table 31.1 Risk factors for VAP

Colonization and aspiration of oropharyngeal and gastric content
Underinflation of the tracheal cuff
Tracheal tube biofilm formation
Sedation
Gastric alkalinization
Supine position
Reduced cough reflex, altered mucociliary clearance
Malnutrition and corticosteroid use
Alcoholism
Antibiotic therapy
Nasogastric tube/enteral feeding
Diabetes mellitus
Severe illness
Immunosuppression
Azotemia

for NIMV success, and the benefit regarding infectious complications depends on the success of NIMV.

There is strong evidence to support the use of NIMV in patients with exacerbation of chronic obstructive pulmonary disease (COPD), acute cardiogenic pulmonary edema, and ARF in immunocompromised patients as well as to facilitate extubation in patients with COPD with a failed spontaneous breathing trial. In selected patients who are good canidates for NIMV and without an immediate need of intubation, NIMV reduces the need for endotracheal intubation and its associated complications. The major advantages of NIMV are fewer nosocomial infections, shorter duration of mechanical ventilation, and lower mortality. NIMV may also reduce nosocomial infections other than VAP as a result of the reduced length of ICU stay and less use of other invasive devices.

Girou et al. performed a retrospective, observational cohort study using prospectively collected data from 1994 to 2001. They reported that a significant increase in NIMV use was associated with improved survival and a reduction in ICU-acquired infections. Also, the rate of ICU-acquired pneumonia decreased from 20 % in 1994 to 8 % in 2001 ($p = 0.04$) [2].

Several studies compared the use of NIMV to IMV or to standard treatment relative to the occurence of nosocomial infections. Hess evaluated 12 studies: four comparing NIMV and IMV; three comparing IMV and patients assigned to NIMV who did not respond and were eventually intubated; and five comparing NIMV and standard therapy [3]. The author reported that in the four studies comparing IMV and NIMV the pneumonia rate was lower with the use of NIMV than with IMV [relative risk (RR) 0.15, 95 % confidence interval (CI) 0.04–0.58, $p = 0.006$]. In additon, in the three studies comparing IMV and patients assigned to NIMV who did not respond and were eventually intubated there was also a benefit with the use of

NIMV (RR 0.24, 95 % CI 0.08–0.73, $p=0.01$). In the five studies comparing NIMV and standard therapy, there was benefit shown for the use of NIMV (RR 0.56, 95 % CI 0.31–1.02, $p=0.06$). When combining the overall data from the 12 studies in a single meta-analysis, the global result was a benefit from NIMV (RR 0.31, 95 % CI 0.16–0.57, $p=0.0002$). The author concluded that in patients who are appropriate candidates for NIMV the available evidence suggests that NIMV is associated with lower rates of pneumonia.

As longer stays on mechanical ventilation and prolonged ICU stays are related to increased risks for nosocomial infections and mortality, early weaning is important. NIMV has been used to facilitate weaning in patients failing spontaneous breathing trials and for patients after planned extubation. Randomized controlled trials have shown that NIMV is an effective method for facilitating weaning but only in a very select group of patients—those with acute exacerbation of COPD [4–6]. In this group, NIMV reduces the duration of intubation, shortens length of stay in the ICU, decreases risk for pneumonia, and improves survival. In a study performed by Ferrer et al., 43 mechanically ventilated patients who had failed a weaning trial for a consecutive 3 days were randomly extubated undergoing NIMV, or they remained intubated following a conventional weaning approach consisting of daily weaning attempts [4]. The authors reported that, compared with the conventional-weaning group, the noninvasive ventilation group had significantly shorter periods of invasive ventilation, ICU and hospital stays, and lower incidences of nosocomial pneumonia (24 % vs. 59 %) and septic shock (10 % vs. 41 %). Similarly, in patients with acute exacerbation of COPD, Nava et al. showed that NIMV during weaning reduces the weaning time, shortens the time in the ICU, decreases the incidence of nosocomial pneumonia, and improves the 60-day survival rate [5].

The use of NIMV in the ICU has been studied extensively, and the optimal location for applying NIMV has been a matter of debate. ICUs offer the most intensive monitoring and therapeutic capabilities in the hospital for patients with ARF. Using the ICU for this application may be impractical, however, because in most countries the number of ICU beds are limited. Also, some patients with ARF are not seriously ill and do not need such close monitoring. In recent years, concern has focused on the use of NIMV outside the ICU (e.g., emergency department, regular hospital ward, respiratory ward). Although there are limited studies about this issue, several have shown that patients with ARF can be successfully treated with NIMV outside the ICU [7–10]. It has also been reported that the use of NIMV in general respiratory wards could theoretically allow earlier use of NIMV during ARF, leading to rapid improvement of physiological variables and a reduction in the need for IMV and its associated complications [10].

In conclusion, the use of NIMV in selected patients who are good candidates reduces the nosocomial infection rate.

Key Major Recommendations

- Nosocomial infections are major causes of mortality and morbidity in ICU patients.
- Endotracheal tube usage is the most important factor for spread of nosocomial infections.
- Noninvasive mechanical ventilation helps avoid the need for intubation.
- Noninvasive mechanical ventilation may reduce the occurrence of VAP and other nosocomial infections as a result of reduced length of ICU stay and less frequent use of other invasive devices.
- Early use of NIMV outside the ICU (e.g., general respiratory ward, emergency department) may reduce the need for IMV and its associated complications.

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Part V

Hospital Organization: Room Organization, Health Professionals, and Prevention

Negative-Pressure and Well-Ventilated Rooms; Bacterial and Viral Filters to the Expiratory Circuit; Personal Protective Equipment for Health Care Workers

32

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Keywords
Ventilated rooms • Filters • Health care workers

32.1 Introduction

Prevention of hospital infection is preferable to treatment in terms of both patient outcomes and costs. One potential source of contamination is the air inside the hospital. There is growing evidence that airborne pathogens that cause some nosocomial infections are seeding widespread environmental contamination, thereby promoting infection in immunocompromised patients. Bacterial and viral filters to the expiratory circuit are recommended for use during mechanical ventilation to prevent cross-infection when breathing systems are used for more than one patient. These important measures to help prevent transmission of hospital infections had hygiene equipment including gloves, gowns, masks, and eye protection.

32.2 Negative-Pressure Rooms or Well-Ventilated Rooms

Nosocomial infections increase the mortality and morbidity rates in hospitals. Transmission through air is an important factor in the spread of nosocomial infections. No guidelines are available on this subject except in the United States and the United Kingdom. Although the studies that have been done to date focused on the ventilation of the operation theaters, intensive care units (ICUs), and isolation

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chambers to decrease the infections, the air in every part of the hospital where patients are cared for should be changed, humidified, and warmed if need be. There are also some opposing views that state the air has no effect on the infections, and optimizing the air is expensive [1].

Methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridium difficile*, and *Acinetobacter baumannii* are transmitted through air. *C. difficile* can persist for 2 days in rooms where elderly patients are cared for even after cleaning the room. For this reason, in areas of the hospital not ventilated properly, environmental and surface cleaning should be done carefully to stop the spread of infections. It should not be forgotten that these surfaces are perfect infection reservoirs [2].

The American Institute of Architects (AIA) guide published between 2001 and 2006 in the United States stated that each patient should be treated in a single room. The air of the patient rooms (AC/h) should be refreshed two to six times per hour. The room humidity and temperature should be 30–60 % and 21–24 °C, respectively. If the sizes of the particles that circulate around the air are >5 μm, they float more slowly and stay floating in the air longer because they are difficult to filtered out by ventilation systems. The particles in the air can be expressed not only by their size but their number of colonies (colony-forming units per millimeter, or CFU/mm) [3]. The most effective method for decreasing spread of nosocomial infections via air is caring for the patients in single, negative-pressure rooms with vertical laminar airflow called "negative-pressure rooms" [1, 2].

Two systems are used to ventilate patients rooms in hospitals. The first system is mixed-type ventilation where air input–output is per square meter. The second is ventilation according to the shifting of the air. The movement of the air changes according to the air coming from outside, the difference in temperature, and the distribution changes according to the site of exhalation. For example, if the exhalation site is low, ventilation is dependent on the horizontal air flow, with the air entering from above [3]. The filters used in the ventilation systems are essential for preventing bacterial contamination in the air. These filters detain water molecules and particles that have spread in the air. The effectiveness of the filters used in hospitals lately is >90–95 % in regard to detaining bacteria. They are also effective in detaining viruses <1 μm. Filters that have the highest effectiveness are called high-efficiency particulate air (HEPA) filters. Although their use is recommended, they are expensive. It is shown that these filters can remove *Aspergillus* spores from the environment. It is suggested that they be used in isolation chambers where immunodepressed patients are being treated [3].

32.3 Bacterial and Viral Filters to the Expiratory Circuit

Mechanical ventilation equipment is a potential vector for the transmission of airborne disease. Precautions must be taken to avoid transmission of pathogenic microorganism between patients. Breathing system filters are recommended for use during mechanical ventilation to prevent cross-infection when a breathing system is used for more than one patient [4]. The Association of Anaesthetists of Great Britain and Ireland recommended in 2002 that a new bacterial/viral filter be used for every

patient. Filters are intended to be used with dry gas. Current international standards do not require the filters to prevent bacterial transfer when it is wet. It is not known whether microorganisms pass through wet filters, but theoretically it might occur. The addition of a bacterial/viral filter at the expiratory side has been shown to prevent contamination of breathing systems. When tested, such filters do indeed reduce the concentration of airborne microbes [5].

Using an adenosine triphosphate (ATP) bioluminescence technique, one study demonstrated that organic soiling of the expiratory side and breathing systems can occur during mechanical ventilation. The use of electrostatic filters cannot be recommended as there is a risk of transmitting contaminated liquid from the breathing system directly into the patient's airway. This is supported by a study in which the levels of contamination were measured in the breathing circle systems used for more than one patient for mechanical ventilation over 72 h with an electrostatic filter between the patient and the breathing system. Contamination was found in 5.6 % of breathing systems after 72 h [4].

32.4 Personal Protection Equipment for Healthy Care Workers

The transmission of health care-associated infections (HCAIs) is a major concern for most health care facilities. It threatens patient safety by contributing to unnecessary suffering and morbidity. Thus, sources of contamination must be reduced to a minimum to reduce prolonged morbidity and health care costs associated with airborne bacteria and other contaminants [6].

Two important measures to help prevent and limit the transmission of HCAIs are hand hygiene and the use of personal protective equipment, including gloves, gowns, masks, and various forms of eye protection. Proper sterilization of instruments, careful preparation of the operation site, and maintenance of fundamental aseptic protocols are all essential to minimizing the infection rate. Hospital personal, especially those in the operating room, are a major source of bacterial contamination.

Bacteriological counts in an unoccupied operating room have been shown to increase significantly when the door to the hallway was not closed properly. Traffic in and out of the operating room should be restricted. The optimum antiseptic agent for the surgical hand scrub has not been established. One study demonstrated that surgical hand scrubs using alcohol-based products are more effective than those using non-alcohol-based agents [7]. Instrument location relative to laminar flow units may play a role in the instrument contamination rate. Suction tips comprise another recognized source as air passes through them, and any airborne bacteria that collect on the suction tip can be transferred to the wound. Surgical gowns and drapes should prevent direct contamination through the gown or by airborne dispersion [6]. There is conflicting evidence regarding the efficacy of face masks in reducing airborne hospital infection. Minimizing conversation when using a surgical mask or hood without a personal isolation suit decreases airborne contamination [6, 7]. The use of double surgical gloves is advisable given that multiple perforations routinely occur during surgical procedures [6].

Key Major Recommendations

- Mechanical ventilation equipment is a potential vector for transmitting airborne disease. Precautions should be taken to avoid transmission of pathogenic microorganisms between patients.
- A laminar airflow ventilation system with a HEPA filter is recommended, especially in the operating room, ICU, and isolation rooms.
- Recent work using an ATP bioluminescence technique has demonstrated that organic soiling of the expiratory side of breathing systems can occur during mechanical ventilation.
- Hand hygiene, donning, and doffing are three important factors for spreading hospital infections.

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Noninvasive Ventilation and Droplet Dispersion: Health Professional Protocols from a Nursing Perspective

33

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Keywords
Noninvasive ventilation • Inhalation therapy • Droplet dispersion

33.1 Introduction

The therapeutic value of noninvasive ventilation (NIV) is well established. It represent a major advance in the possibilities of ventilatory support of patients with respiratory problems [1]. Over the last two decades the use of NIV has increased gradually in patients with acute respiratory distress based on relevant scientific research and clinical practice guidelines published by their scientific communities [2].

The use of inhalation therapy is normally associated with the patient's NIV, where success is associate. In these patients there must be a need for effective bronchodilation or they may be suffering from acute or chronic respiratory distress. Usually, inhalation therapy is associated with stabilizing patients with asthma, chronic obstructive pulmonary disease (COPD), or other respiratory diseases [3, 4].

Inhalation therapy has assumed a prominent place in controlling bronchial obstruction (Rubin 2012), particularly in people undergoing NIV, which allows more rapid onset of action and greater therapeutic efficacy with low doses [5]. Thus, selecting the correct inhalation technique requires involvement of the patient as well as the respective caregivers who assume the point of view of caregivers, a pivotal role in

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reducing health care costs [6]. It should also improve quality of life (Smith and Grose 2012), with an impact on outcomes regarding the need for nursing care [7–9].

The primary goal of proper inhalation technique is deposition of drug particles in the airway. This may be difficult because there is a variation between the fraction generated by the device, that inhaled by the patient, and the fraction that is deposited in the lung [9]. Factors that influence drug deposition in the lung are particularly the particle size, the breathing pattern of the patient, the anatomical airway (Rubin 2012), and the inhalation technique used [10].

Scientific evidence shows the correct particle deposition in the lungs will reduce the number of exacerbations, thereby reducing the need to use mechanical ventilation (MV) and endotracheal intubation [9, 10]. The symbiosis of inhalation therapy and use of NIV has demonstrated superior results in patients with hypoxemic respiratory failure. It has reduced the number of complications (e.g., pneumonia and other co-morbidities) [3, 4]. Clearly, though, nursing care is essential in the hospital and when planning domiciliary NIV in association with inhalation therapy.

This chapter describes the factors that influencing particle deposition in the airway. It also establishes a protocol for use in patients on inhalation therapy plus NIV and their caregivers based on scientific evidence available worldwide over the past decade.

33.2 Definitions

Inhalation therapy consists of the deposition of particles in the airway. The aim is to deposit an adequate dose in the lower airways (maximizing its therapeutic effect) and a higher local concentration to minimize systemic absorption and side effects [11]. At the hospital, during exacerbation of pulmonary distress, respiratory inhalation therapy consists of a bronchodilator to effect relaxation of bronchial smooth muscle and relief of the dyspnea [12]. The particle size is important and should be an aerosol.

An *aerosol* is a set of small particles, solid or liquid, that are dispersed in a gas (generally air). The effectiveness of an aerosol is closely linked to the amount of drug deposited and the location of the deposition. The particles are deposited in the airway via four mechanisms: inertial impact, gravitational sedimentation, diffusion, inhalation technique [10].

Noninvasive ventilation is mechanical ventilation by mask or other interface without resorting to inserting an invasive artificial airway, such as an endotracheal tube, or performing a tracheostomy [13]. NIV, by applying pressure support—positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP)—through a nasal or facial mask, reduces the work of breathing and the respiratory rate. It optimizes gas exchange by recruiting alveolar tissue [14] and allows a tidal volume increase.

33.3 Results Sensitive to Nursing

Results sensitive to nursing care are defined as nursing care targeted to the needs of individuals or a group in regard to their health. These factors are based on organizational experience and a high level of knowledge. They have a direct impact on

functional status, self-care, symptom control, safety, adverse occurrences, and customer satisfaction. These results also contribute to developing the quality framework proposed by Sidani and Doran [15]. They comprise patient variables (age, sex, education, type of illness, adverse occurrences, co morbidities) and nursing variables (level of education, experience, patient/nurse ratio, organization, workload). This process includes independent actions (nursing interventions) and interdependent actions (team communication, coordination, case management) [15].

Nursing care consists in providing care with safety, quality, ethics, and collaboration through an individualized process that is planned and designed based on the best evidence available. The aim is to produce positive results that reflect the optimal health patient, reducing symptoms and preparing and maintaining patients in their homes at highest level of care [15].

Personal preferences, convenience, ease of use, and economic factors can affect treatment efficacy, treatment adherence, and disease control. Education programs for children and adults play a central role in helping patients to use their inhalation devices correctly [16]. Incorrect use of inhalation devices may result in inadequate treatment of the respiratory disease [17].

There are several devices available for inhalation therapy, making it possible to deliver drugs in various forms. In this context, the aerosol particles of medication must be inhaled correctly so the distribution and absorption into the pulmonary mucosa are optimal, producing a rapid therapeutic effect (e.g., dilation of airways after inhaling a bronchodilator or reduction of inflammation of the airways after inhaling a corticosteroid) [10].

33.4 Methodology

To define a wide range of assumptions inherent in the problem described and delineated meet the goal, we prepared the following initial question, which meets the criteria of the PICO format [18]: For persons in programmed NIV, what factors influence particle deposition (inhalation therapy) at the level of the respiratory system through the perspective of nursing care?

By setting the target object of study, one can again broader understanding of this phenomenon by carrying out a survey of electronic databases. We surveyed EBSCO (CINAHL plus with full text, MEDLINE with full text, Nursing Reference Centre, Cochrane Database of Systematic Reviews). The keywords used were guiding [(positive pressure ventilation *or* continuous positive airway pressure *or* noninvasive ventilation) *and* (nebulizers and vaporizers *or* air movements *or* droplet dispersion) *and* (intervention *or* nursing *or* nursing outcome)].

Inclusion criteria favored the articles based on the issue of persons undergoing NIV inhalation therapy and those that used qualitative methodology and/or a quantitative or systematic literature review to identify the results sensitive to nursing care. Exclusion criteria were all items repeated in databases, those dated prior to 2002, and those not correlated with the object of study. This gave a total of 21 articles that were analyzed and that later underwent critical evaluation and systematization of the knowledge.

33.5 Discussion

An inhaler is a device that enables administration of drugs directly to the airways in the form of an aerosol. Inhalers are indicated for the treatment and stabilization of asthma, COPD, and other respiratory diseases [7]. Currently, there are several types of inhaler, each with particular characteristics and different management techniques, including the controlled pressurized metered dose inhaler (MDI), the pressurized metered dose inhaler (pMDI), the dry powder inhaler (DPI), and nebulizer systems [8].

The pMDIs are devices containing a drug and a propellant gas compressed under high pressure that, when activated manually by the individual, releases the drug into the airways in the form of an aerosol [7, 8]. The dose of the aerosol is fixed and controlled. Its particles are initially large, but evaporation of propellant reduces their diameter, making them breathable [10]. As only particles with diameters 0.5–2.0 μm reach the lower airways and alveolar tissue, deposition of a drug in the lungs obtained from an MDI, on average, reaches 10–80 % of the oropharynx [7–9]. For the MDI to be effective and reach the lower airways, efficient coordination between activation of the device, use of a correct inhalation technique, and a high inspiratory capacity of the individual are required [19].

Maximizing the amount of drug inhaled and decreasing its deposition in the mouth calls for difficult bridging hand–lung coordination during use of the MDI. Resort to use of a spacer accessory may be necessary [7]. The spacer coupled to the MDI allows early evaporation of the propellant and consequently reduces the particle size of the aerosol, rendering the particles capable of reaching more distal areas of the airways [10]. When there is deceleration of the aerosol, it provides a longer period of time for the subject to inhale the drug, with reduced impact and oropharyngeal deposition, thereby increasing lung deposition and the efficacy of drug therapy [7]. However, because the expander chamber has static charges that attract the suspended particles to the walls, reducing the amount of inhaled drug delivered, it must be serviced daily to reduce resistance and to ensure effective administration [7–9]. Given the diversity of formats of the spacer devices on the market, they should be selected according to the characteristics of each patient, including his or her lung capacity and ability to coordinate inspiration with activation of the inhaler. In tracheostomized patients and/or undergoing ventilation (invasive or noninvasive) the spacer devices can be an asset and during administration of inhalation therapy should be tailored to the ventilator breathing circuit [5].

The MDI has major advantages, including its low cost, its portability, and the possibility of use with the spacer device for optimal inhalation [8]. In patients with less hand-lung coordination and inspiratory speeds below those required for effective use of the MDI system, the Autohaler may be used, which releases a pressurized solution at a fixed dose, but whose activation is caused by the patient's inspiratory flow.

The DPIs release the drug to the airways in the form of dry powder, and their activation is automatically generated by the inspiratory flow of the patient [9]. They do not have a propellant, do not require manual activation, and can adapt to patients who lack manual dexterity and strength for triggering the MDI [7]. The effectiveness of DPIs is guaranteed only in patients with a high inspiratory capacity, reducing pulmonary deposition before low inspiratory flow [19]. This particularly relates to the fact that the inhaler has internal resistance, and the individual must be able to overcome it with a deep breath to activate the device [7]. When performed properly, all of these devices allow the drug to be deposited in 12–15 % of the lung.

Currently, there are devices that give a single dose (Aeroliser and HandiHaler) and those that provide multiple doses (Turbuhaler and Diskus). Unidose devices must be loaded with capsules containing the drug at each use. The multidose devices contain several doses and are always ready for use (until all the doses are inhaled) [11].

Inhalation profile recorders (IPRs) are environmentally safe and have emerged to fill the incorrect use of MDIs due to difficulty with hand–lung coordination. IPRs are characterized by being easy to carry, easy to use, and having a dose counter (multidose) [11, 19].

The nebulizer systems are devices that produce an aerosol from an aqueous solution. There are two types: jet (pneumatic) or ultrasonic. The jet nebulizers have a source of gas (air/oxygen compressor tablet or laptop) and a spray chamber where the aerosol is produced [19]. The passage of air/oxygen, compressed by a small pipe or chamber holding the liquid solution, causes its suction from the reservoir and produces the aerosol [7–10].

Nebulizers always have an ultrasonic generator and an electronic transducer. The aerosol is produced by thevibration of a quartz crystal, emitting ultrasonic waves to the surface of the liquid solution, thereby creating the aerosol [11, 19]. This type of device requires less patient coordination compared to MDIs and DPIs as inhalation of the drug is performed passively during tidal volume breathing by the patient. Thus, it does not require patient coordination with the unit [5–19]. The aerosol is administered by a face mask placed over the mouth and nose of the patient and requires the cooperation of the patient only to keep the mask in place [7]. Regarding lung deposition, 40 % of the dose is lost in the residual volume nebulizer and 30–50 % in the environment [19]. Nebulizers have fundamental advantages as they can reverse severe bronchial obstructions with lower inspiratory flow rates and can “adapt” to the patient’s breathing pattern. However, they are more difficult to use, have less portability, have continuous flow during inspiration and expiration (which leads to wastage of the drug during expiration), require more time to reach the end (5–10 min), and requireds frequent maintenance [7, 19].

For better understanding of the various inhaler devices, Table 33.1 shows their main advantages, disadvantages, and their intended populations.

Table 33.1 Potential advantages and disadvantages of each type of device

Devices	Population	Advantages	Disadvantages
pMDI	Age >5 years (if <5 years, use with a spacer chamber or Aerochamber) Requires a slow inhalation and coordination "hand-lung" during their activation. It can be difficult to perform on children and elderly people	Portable and compact Ready to use Low price No contamination of the contents High levels of lung deposition (> 50 %) Can be used with mechanical ventilation	Need coordination between activation and inhalation High oropharyngeal deposition Requires apnea Possible effect "cold Freon" Upper limit for the content of unit dose Difficulty determining the number of doses available
MDI coupled to a spacer chamber	Age >4 years (<4 years, valvular camera with face mask) Indicated for patients who have difficulty in carrying out the proper technique of MDI	Ready to use Require less administration time Reduced need for coordination Technical administration less critical due to the reservoir effect Reduction of oropharyngeal deposition	Increased complexity in administration for some patients Increases of costs and decreases the portability compared with the MDI Increased static charge may attract the particles to the walls of aerosols and reduce pulmonary deposition The mechanism of action can change the properties of aerosols compared with the simple MDI
Autohaler	Age >5 years It can be useful in patients unable to coordinate inhalation with activation and in elderly patients	Patients unable to coordinate inhalation and activation Elderly Minor variation in the dose emitted due to reproducible performance	Patients may incorrectly stop inhalation in the activation of the device Cannot be used with spacer device
DPI	Age>4 years Most children with ages <4 years cannot generate an effectively inspiratory flow	Minor coordination compared with pMDI No propellants Portable and compact Requires less administration time Ready to use (multidose) Counters of doses in multidose	Some devices are single dose and require preparation Can be confused with oral medications Loss of dose if the patient exhales through the device May result in the deposition in the oropharynx Upper limit for the content unit dose Cannot be used with mechanical ventilation

Table 33.1 (continued)

Devices	Population	Advantages	Disadvantages
Nebulizers	Can be used at any age	It requires coordination of the patient Possible of administering multiple drugs Change of the dose as needed Can be used at any age	Lack of portability (jet nebulizers) Longer treatment Stricter standards of cleanliness, with an increased chance of contamination Unavailability of some drugs for administration Variability of performance efficiency between different nebulizers Less effective than other devices (Waste) More expensive (ultrasonic nebulizer) Mask must adapt accordingly

Adapted from [20, 21]

The percentage deposition of a drug to the lungs varies according to the type of inhaler device used as well as the use of a correct administration technique [5]. The physical characteristics of aerosol particles—size, density, electrical charge, hygroscopicity, shape and velocity of the aerosol—have an impact on the deposition. These characteristics are dependent on several factors, including the drug to be used, its formulation, and the device. These characteristics are relevant because among the various physical characteristics the size of aerosol particles is the most important factor for deposition of the drug in the lungs [22].

Moreover, an aerosol composed of more aerodynamically shaped drops is likely to be associated with higher penetration. Finally, the speed at which the aerosol is generated also affects the fraction delivered to the lower airways. Aerosols generated at a very high speed tend to be deposited in the upper airways and the supply to the lower airways is compromised [22].

The patient characteristics are factors affecting primarily the release of drug aerosol into the lungs. Examples are those relating to ventilation and the respiratory state of the patient. Ventilatory factors include the (1) inspired volume, (2) inspiratory time, (3) duration of apnea, and (4) delivery time of the aerosol during inspiration. The inspired volume plays a critical role in nebulized drug delivery. With the increased volume of inhalation, the particles are more likely to be carried deeper into the lungs. Thus, patients are instructed to make a deep inspiration with the performance of the aerosol delivery device and exhale to functional residual capacity (FRC) before starting the inspiration [20–22].

It has also been shown that apnea is important for maximizing drug delivery because it increases penetration and the number of particles deposited in the lungs. For administration of inhalation therapy to patients undergoing NIV, there is evidence indicating the use of pMDI device with a spacer device or jet nebulisers would be best. It allows greater deposition in the lung and reduced deposition in the ventilator circuit. However, there are specific factors that influence the deposition of particles in the NIV, so it requires a specific inhalation technique [23]. Administration of an inhaled drug in the patient on NIV is complex. It can be done by disconnecting the patient's circuit (if possible) and then using pMDI and a spacer device. Ideally, however, the patient continues NIV, particularly in situations of severe dyspnea and hypoxemia [23].

Dhand (2012) analyzed the main factors that influence patients undergoing inhalation therapy along with NIV. The ventilator fans are different in portable units used in the ICU and those used for home care. They have evolved to also allow better efficacy. The use of bilevel pressure support allows several physiological improvments as well as a reduced particle size with consequent greater deposition of the aerosol. In relation to CPAP, this has produced two setbacks. On the one hand it has reduced the size of the particles but on the other hand the effectiveness of the jet nebulizers is diminished. The circuit for avoiding rebreathing carbon dioxide is still a concern. In addition to ICU ventilators, the CPAP ventilator has only one circuit for both inspiration and expiration, which can cause losses and deposition of drug. Currently, the choice of interface is varied, but to reduce losses of drug and possible irritation of the ocular mucosa, a face mask is recommended.

With regard to humidity, the results are similar for invasive and noninvasive ventilation. Evidence shows that with circuit humidification there is an approximately 40 % reduction in drug delivery in pressurized devices such as nebulizers because of the increased particle size and their compaction. The principles of using humidification go against the premise of inhalation therapy, and the benefit of its concomitant use is contraindicated. It is required for suitable humidity that results in increased comfort and tolerance for the patient, thereby enhancing the effect of the bronchodilator drugs [23].

Regarding the gas used for the NIV, the latest research suggests the use of a gas less dense, heliox (helium + oxygen), which results in increased effectiveness of NPPV in reducing the work of breathing. The use of heliox for inhalation therapy reduces particle deposition in the airway and increases the pulmonary level. This return is recommended for use with a nebulizer jet flow rate of 6–8 L/min.

There is no doubt that for delivery of certain drugs pressurized inhalers with a spacer device in the ventilator circuit and jet nebulizers have superior effects.

An important aspect is the local adaptation of the devices in the circuit, which still do not meet consensus.

The NIV patient characteristics also determine if there is greater or lesser particle deposition in the lungs. The main points to be noted are related to the severity of the underlying disease, tolerance to NIV, the interface, synchronization with the ventilator, and what is needed to coordinate with the inspiratory phase of the respiratory cycle.

Although administration of inhalation therapy to the patient connected to NIV is most effective, there are situations where the patient can be disconnected from the NIVcircuit to administer their inhalation therapy, especially during breaks and rest periods prescribed in several of types NIV (e.g., NIV only at night). In these situations, the administration technique is similar to the technique used for applying inhalation therapy at home. Selection of the type of inhaler should thus be patient-centered, seeking to offer the greatest therapeutic benefit and adapt to the patient's individual needs [19]. For treatment with aerosol therapy at home, the availability and characteristics of the devices, the preferences of the patient, and his or her age, lung capacity, clinical status, manual dexterity and strength, lifestyle and socioeconomic conditions (cost/benefit) should guide the choice of the device [20, 21].

Regardless of the type of inhaler selected and the duration of treatment, correct use of the devices by the patient assumes fundamental teaching and measurement of consistent inhalation [19, 21]. Health professionals, who must have familiarity with the various inhalers and associated devices, should be familiar with proper handling of the devices. They can then teach and demonstrate to the patient the correct way to use the device of choice [12]. Furthermore, the technique for using inhaled medication must be constantly reevaluated as some patients do not perform the technique properly, even after several counseling sessions. Thus, an appropriate technique may become inadequate over time [19, 23].

Once the respiratory disease is controlled with the correct use of inhaled medications, it is essential that practical measures are taken to minimize errors and increase the effectiveness of the medication. Various measures, such as revaluating the adequacy of the patient's inhalation technique. Although patients claim to know the right technique, a practical reevaluation by the health care team may prove otherwise. In that case, after medical consultation, short- or long-term educational programs can be implemented [12, 24, 25].

It is assumed as critical that nurses have adequate training in aerosol therapy and its guidelines to optimize the benefits for patients in the hospital or clinic (Table 33.2). They can use the levels of scientific evidence according to the Oxford Classification Centre for Evidence-based Medicine Levels of Evidence 2011 (2011).

Table 33.2 NIV-Droplet dispersion

Process of care	Procedure/justification			Author/level evidence	Degree of recommendation
Information collection and preparation	Hand hygiene		Prevent transfer of microorganisms if there is a risk of exposure to bodily fluids	[24, 25]	Level II
	Identify patient		Individualization of care process	[22]	Level III-1
	Presentation and brief explanation of the procedure and benefits of aerosol in combination with NIV		Assess whether the client/family requires special considerations regarding communication (e.g., due to illiteracy, language barriers, deafness); take steps to meet those needs, if present Assess the client/family to the deficits of knowledge and anxiety about aerosol Reassure the client/family and provide information and emotional support when needed	[7, 22, 24, 25]	Level III-1
Planning	Assess the patient's respiratory status		Monitoring the vital parameters and oxygen saturation Observe signs of increased respiratory effort and ask the patient if he feels difficulty in breathing	[7, 19, 22, 24, 25]	Level III-1
Execution	Patient connected to NIV	Providing aerosol by nebulizer	Minimize leakages in the circuit and mask and ensures good synchronization client/ventilator Adapting the nebulizer circuit (following the manufacturer's instructions) between the exhalation valve and the mask, at least 15–18 cm from the patient Add the prescribed medication Use as interface a facial mask Assist the client in acquiring a comfortable position to sit in bed or a chair to promote maximum efficiency of breathing Connecting to an external continuous flow of 6–8 L/min. Make sure that the mist that is created is flowing through the tube and into the mask Keep monitoring of NIV with control of volumes, leak and level of oxygenation Maintain the prescribed medication in aerosol throughout the period of time indicated by the attending clinician, the protocol facilities, and/or manufacturer's instructions When the aerosol is complete disconnect the nebulizer, remove it from the circuit and carry out cleaning according to the manufacturer's instructions Monitoring patient response to the respiratory parameters and possible adverse effects	[7–9, 19, 22]	Level III-1

		Provide aerosol by inhaler (pMDI)	Review the manufacturer's instructions with the patient and team about to activate the prescribed inhaler Explain the procedure to the patient and its importance Minimize leakages in the circuit and mask, and ensure a good synchronization patient/ventilator Stir the pMDI and warm to hand temperature. Adapting appropriate spacer device in the ventilator circuit, between the ventilator and the mask Do not turn off the humidifier Adapte the pMDI and coordinate the discharge with the onset of inspiration Wait at least 15 s between discharges (puffs) and others inhalers Remove the pMDI and close the circuit Monitor the patient response to the respiratory parameters and possible adverse effects	[7, 19, 22, 24, 25]	Level III-1
	Patient disconnected from the NIV	Provide aerosol by nebulizer	Place the drug dosage to be administered in the chamber along with a saline solution (if indicated) Connect the nebulizer to the mouthpiece or mask Help the patient to acquire a comfortable position that favors the respiratory ventilation Connect the nebulizer tube to the oxygen ramp Hold the nebulizer in an upright position to prevent spillage and losses When the fog starts, the patients should inhale slowly and deeply Continue until the product finishes, that is when the fog begins to decrease (5–15 min)	[8, 9, 19, 22, 24, 25]	Level III-1

(continued)

Table 33.2 (continued)

Process of care	Procedure/justification			Author/level evidence	Degree of recommendation
		Provide aerosol by pMDI	Stir the inhaler Hold the inhaler vertically Gently exhale the residual functional capacity and perform the administration, preferably standing or sitting with the head held high Preferably, adapt the pressurized inhaler in the spacer chamber and put the mouthpiece in the mouth between the teeth With the onset of the inspiration, operate the inhaler Inhale slowly to reach the maximum capacity Hold the breath for 10 s, if possible Wait, if possible, at least 60 s between doses ("puffs") prescribed If it's for use without a spacer chamber is required a inspiratory flow ≥ 30 L/min	[8, 9, 19, 22, 24, 25]	Level III-1
		Provide aerosol by DPI	Check that the device is clean and functional Activate or set a dose the device according to the instructions Perform the administration preferably standing or sitting with head held high Place your lips on the mouthpiece sealing around it, taking care not to block the device with the tongue Breathe in quickly and deeply through the mouth to activate the flow of the aerosol Remove the device from your mouth and hold your breath for 10 s (or as long as is comfortable)	[8, 9, 19, 22, 24, 25]	Level III-1
	Both situations	Discard disposables materials used according to installation protocols and follow the protocols for cleaning and storing the nebulizer and other devices Discard the materials used in the procedures according to installation protocols Perform hand hygiene		[22, 24, 25]	Level III-1

Evaluation	Register the administration of the aerosol to the patient, including the time and date expected, name, dose and type of aerosol, and devices provided Record any unexpected events that occurred, interventions and outcomes for the patient (e.g., respiratory status) Give special attention to the continuity of care in the education of patient/family	[8, 9, 19, 22, 24, 25]	Level III-1
Patient and family education	Educate the patient/family about what to expect during and after the aerosol If the patient is or will be cared at home or after discharge, explain, demonstrate and ask for demonstration of the administration technique, as well as the resolution of the most frequent problems Provide the team contact Educate about clinic signs and symptoms that may indicate the development of complications after the aerosol and that should be reported immediately to the doctor. This signs and symptoms include shortness of breath, anxiety and/or fear due to difficulty in breathing Explain the importance of keeping the follow-up appointments, to allow the continued medical surveillance of the patient's condition Provide written information to reinforce verbal learning	[8, 9, 19, 22, 24, 25]	Level III-1

Guideline for aerosol in patients with noninvasive ventilation (NIV)

Key Major Recommendations

- Inhalation therapy plays a crucial role in controlling bronchial obstruction in that it allows smaller dosages that produce faster, more effective therapeutic action.
- Their effectiveness depending on the ventilatory pattern and the anatomical airway of the patient, the inhalation device used, and the use of correct technique of administration.
- Inhaler devices available today are metered dose inhalers (MDIs), pressurized metered dose inhalers (pMDIs) associated or not with the use of spacer device; dry powder inhalers (DPIs); and nebulizer systems.
- Each device has unique characteristics and management techniques. When selecting an inhalation device, one should take into account the clinical picture and the patient's age and skills/capacity, utilization, cost/benefit, and duration of treatment, among others. The operator should seek the inhaler that most responds to the individual needs of each patient and offers the greatest therapeutic benefit.
- Achieving these therapeutic benefits requires use of a technique appropriate for administering the inhalation. Thus, standardized teaching and monitoring by the medical and nursing staff is fundamental.
- The importance of health education is paramount for transfering skills so the patient can adapt to the therapeutic inhalation therapy regimen and improve his or her state of health and quality of life.

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Preventing Airborne Disease Transmission: Implications for Patients During Mechanical Ventilation

34

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Keywords
Aerosol-generating procedures • Noninvasive ventilation • Personal protective equipment • Health care workers

34.1 Introduction

The organisms causing respiratory infections such as influenza are spread in droplets or aerosols or by direct or indirect contact with contaminated surfaces. Certain medical procedures have been termed aerosol generating because they are associated with high or augmented inspiratory and expiratory flows, which can increase microbial dissemination. Invasive ventilation maneuvers and noninvasive ventilation (NIV) fall into that category. We discuss the risk of transmitting these procedures and the strategies for mechanical ventilation in future airborne epidemics with special consideration given to the issue of protecting health care workers (HCWs).

34.2 Analysis of the Problem

Pathogens in the air are spread on particles or droplets. The solid matter may come from skin, and the droplets may be generated from the upper or lower respiratory tract, mouth, or nose and under such circumstances as vomiting, dripping water taps, and diarrhea. Respiratory droplets, which can carry microorganisms such as bacteria and viruses, constitute a medium for the transmission of infectious diseases. Droplets from the nose and mouth contain bacteria but do not travel >2 m.

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The concept of airborne transmission and large droplet transmission is based on droplet size. The classic study of airborne transmission by Wells revealed the relation between droplet size, evaporation, and falling rate. It was determined by studying the evaporation of falling droplets and is referred to as the Wells evaporation-falling curve of droplets. Wells postulated what is now a widely accepted hypothesis of the distinction between droplet size and airborne transmission routes.

Small droplets start to evaporate after release, and thus change their size resulting in droplet nuclei that are sufficiently small to remain suspended in air for a long time and still be infectious. Large droplets (>100 μm) can settle on the ground before they become droplet nuclei [1, 2]. Most respiratory droplets are <100 μm in diameter and evaporate rapidly in the surrounding environment. They become droplet nuclei, which are suspended in the air or are transported away by airflow. The size distribution of droplets is a matter of great debate, but in general various particle sizes are generated: large droplets (>20 μm) that fall directly to the ground or surface; medium-sized particles (5–20 μm), fall at a slower rate or remain temporarily suspended by air currents and evaporate; to become droplet nuclei (aerosol) particles <5 μm in diameter, which remain suspended for longer periods of time [1, 2]. Studies have demonstrated that particles <10 μm in diameter are more likely to cause infection in the lower respiratory tract [3, 4]. The suspension of these droplet nuclei may cause infection over greater distances and increase the duration of infection risk following generation of the initial respiratory aerosol. In addition, the concentration of particles in the secretion and the infectious dose of the pathogen affect the risk of infection. Droplets in the respirable range (~5 μm) may play a significant part in transmission. A few studies have quantified the viral load in droplets or aerosols [5].

An observational study [6] of influenza A and influenza B in exhaled breath showed viral RNA in one-third of infected patients. Also, 99 % of the particles had a diameter <5 μm when sampled during tidal breathing. Although some individuals recover from seasonal or H1N1 influenza after having experienced minimal symptoms, a subgroup of high-risk patients develop complications, including respiratory failure. With the appearance of more pathogenic strains, such as H5N1, respiratory insufficiency may occur in >50 % of those affected. These patients are managed with antiviral therapy and antibiotics for secondary bacterial pneumonia. However, but the mainstay of management is supportive respiratory care, which includes titrated oxygen therapy for hypoxemic patients and ventilatory support for those with respiratory insufficiency [7, 8].

In contrast to the situation regarding severe acute respiratory syndrome (SARS) or tuberculosis prevention in HCWs, little attention has been given to the importance of HCWs personal protective equipment (PPE) (gowns, gloves, masks) for prevention and management of influenza. This situation has arisen because vaccination of HCWs has been shown to reduce or prevent nosocomial transmission. It seems prudent for nonvaccinated workers to wear N-95 masks, particularly during high-risk procedures or with very ill patients. There is limited evidence that upper-air ultraviolet light is effective in reducing influenza transmission rates.

Some medical procedures have been termed aerosol-generating procedures (AGPs) as their most common feature is that they are associated with high or

augmented inspiratory and expiratory tidal flows, which may increase viral aerosol dissemination. The list of AGPs [5] include bronchoscopy, airway intubation, and invasive ventilation maneuvers such as open suctioning, cardiopulmonary resuscitation, NIV, and continuous positive airway pressure (CPAP) therapy, high-frequency oscillation ventilation, and induction of sputum. Certain other procedures, such as delivery of nebulized medication therapy and high-flow O_2, are considered possible aerosol generators but of lesser infective risk. There is an association between some of these AGPs and an increased incidence of SARS in HCWs with super-spreading events on the wards [9].

Much of the evidence for the link between AGPs and increased transmission of respiratory viral infection was generated during the SARS epidemic. In Toronto, China, and Singapore, HCWs constituted approximately 20 % of the critical care cases. Infection rates were higher in doctors and nurses carrying out endotracheal intubation [relative risk (RR) 13.29, 95 % confidence interval (CI) 2.99–54.04, $p=0.03$], and nurses caring for SARS patients receiving NIV may have been at increased risk (RR 2.23), but these findings did not reach significance [95 % confidence interval (CI) 0.25–21.76, $p=0.5$] [10]. In a case–control study of the dissemination of SARS from an index case to other patients on the same ward, Yu et al. [9] showed an increased risk associated with the index patient requiring oxygen or bilevel NIV. Case reports [11, 12] have also linked transmission of infection to nebulizer use in the index patient. However, patient variables are also important factors to consider: Sicker patients have a higher viral load and are more likely to require oxygen and ventilator support, and those with underlying asthma require nebulizer therapy and cough more because of airway hyperreactivity. Both settings increase the risk of aerosol transmission.

There is additional evidence concerning AGPs and the risk they present to HCWs. Experimental studies that have investigated airflows around oxygen masks and during NIV [13–18]. These studies used human simulator models or normal subjects mimicking respiratory distress. Hui et al. [16] examined smoke particle dispersion from the lungs of a human simulation model receiving oxygen therapy, frequently used in the treatment of patients with respiratory failure. The authors found that a jet plume of smoke could be generated from exhaust holes up to 0.45 m from the mask. Although this model provides a visual image of smoke aerosol behavior, and the possible zone of transmission risk, it is not necessarily representative of the behavior of a respiratory aerosol and infectious particles contained therein.

Two similar studies were carried out on oxygen masks. One indicates that oxygen mask usage might contribute to droplet-respiratory transmission of SARS [14]. The other observed a visible range of the smoke plume of 0.08–0.40 m depending on the type and flow rate of the mask used [19].

Simonds et al. [20] evaluated the characteristics of droplet/aerosol dispersion around delivery systems during NIV, O_2, nebulizer treatment, and chest physiotherapy by measuring the droplet size, geographical distribution of droplets, decay in droplets over the time after the intervention was discontinued, and the impact of modifying the NIV circuit in clinical practice. Three groups of patients were studied: normal control subjects; subjects with coryzal symptoms; adults with chronic

lung disease who were admitted with an infective exacerbation. Each group received O_2, NIV using a vented mask system, and a modified circuit with a non-vented mask and an exhalation filter. All received nebulized saline and a period of standardized chest physiotherapy. Droplet counts in mean diameter sizes ranging from 0.3 to >10.0 μm were measured with a counter placed adjacent to the face and at 1 m distance from the patient at the height of the nose/mouth of an average HCW. NIV using a vented mask produce large droplets (>10 μm) in patients ($p=0.042$) and coryzal subjects ($p=0.044$) compared with baseline values but not in normal controls ($p=0.379$). This increase in large droplets was not seen using the NIV circuit modification. Chest physiotherapy produced droplets predominantly >10 μm ($p=0.003$), with the droplet count (as in the NIV patients) falling significantly by 1 m. O_2 did not increase the droplet count in any size range. Nebulized saline delivered droplets in the small and medium size aerosol/droplet range, in keeping with the specified performance characteristics of the device, but did not increase the large-droplet count. Preliminary analyses suggest that droplet counts fall to within a baseline range within 20–40 min of discontinuing the NIV and chest physiotherapy.

In conclusion, NIV and chest physiotherapy are droplet- (not aerosol-) generating procedures, producing droplets >10 μm. Because of their large mass, most fall on local surfaces within 1 m. The only device producing an aerosol was the nebulizer. The output profile is consistent with nebulizer characteristics rather than dissemination of large droplets from patients. These findings suggest that HCWs who are providing NIV and chest physiotherapy and are working within 1 m of an infected patient should have a high level of respiratory protection. Infection control measures designed to limit aerosol spread (e.g., negative-pressure rooms) may have less relevance.

Tran et al. [21] systematically reviewed the literature regarding the risk of transmitting acute respiratory infections to HCWs exposed to patients undergoing an AGP compared with the risk of transmission to HCWs caring for patients not undergoing an AGP. The outcome of interest was the risk of acute respiratory infection. They identified five case–control and five retrospective cohort studies that evaluated transmission of SARS to HCWs. The procedures reported to present an increased risk of transmission included tracheal intubation [$n=4$, cohort: odds ratio (OR) 6.6 (2.3–18.9); $n=4$, case–control study: OR 6.6 (4.1–10.6)] and NIV [$n=2$, cohort: OR 3.1 (1.4–6.8)]; tracheotomy [$n=1$, case-control: OR 4.2 (1.5–11.5)]; and manual ventilation before intubation [$n=1$, cohort: OR 2.8 (1.3–6.4)]. Other intubation-associated procedures, endotracheal aspiration, suction of body fluids, bronchoscopy, nebulizer treatment, administration of O_2, high-flow O_2, manipulation of O_2 masks or bilevel positive airway pressure (Bi-PAP) masks, defibrillation, chest compression, insertion of a nasogastric tube, and collection of sputum were not significant. These findings suggest that some procedures potentially capable of generating aerosols have been associated with increased risk of SARS transmission to HCWs or were a risk factor for transmission. The most consistent association across multiple studies was tracheal intubation. The results of this report should not be generalized to all acute respiratory infections because the evidence available is strictly limited to SARS.

Noninvasive ventilation and continuous positive airway pressure are likely to play a minor role in the management of moderate to severe acute lung injury caused by influenza or secondary bacterial pneumonia, or in patients with multisystem failure. However, NIV was used successfully in some SARS cases [22]. There is also potential for NIV to reduce the need for intubation in patients with influenza pneumonia or chronic respiratory disease, facilitate extubation, and widen the provision of ventilator support outside the intensive care unit (ICU). It may also be used as ventilator care in patients with chronic obstructive pulmonary disease, congestive cardiac failure, and other serious co-morbidities. NIV is sometimes used to palliate symptoms in those with end-stage disease in whom ICU admission is not indicated [23]. These indications should be set against the risk of droplet dissemination during the delivery of NIV. Despite the study of Simonds et al. [20], which indicated that NIV generates large droplets adjacent to the patient that fall significantly at 1 m from the patient, and that adding a circuit using a nonvented mask plus a filtered exhalate reduces the number of large droplets produced, there is still concern about dispersion of infectious particles. Nevertheless, in a Hong Kong hospital where more than 20 patients were placed on noninvasive positive ventilation, all HCWs on the ward performed meticulous infection-control procedures and used PPE. Despite the intense exposure, none became infected with SARS [24]. Patient selection is important for NIV as it has not been shown to improve the mortality rate among patients with acute respiratory distress syndrome (ARDS) and may be not suitable for patients in whom short-term improvement is not expected [25, 26].

Protection of the HCW during mechanical ventilation includes isolation of infected patients, use of PPE, and strict hand hygiene by all. The World Health Organization and the Centers for Disease Control and Prevention have issued guidelines that recommend the use of standard, contact, and airborne protection, including respirators of N-95 standard or higher, which filter at least 95 % of particles that are ≥1 mm with <10 % face seal air leak. These filters not only protect against virus-transmitted diseases but also against tuberculosis (TB), filtering at least 95 % of the 3- to 5-mm TB bacilli out of the air inhaled by HCWs. The need for N-95 masks depends on the mode of transmission. If transmission is solely by droplet, face shields, eye protection, and surgical masks are adequate. However, if transmission is airborne, N-95 masks should be used. As reviewed earlier, there is evidence that airborne transmission of SARS occurred, at least from the super-spreaders or during aerosol-generating activities such as intubation or suctioning. Knowing that super-spreaders are identified only in retrospect, it may be prudent for workers to wear N-95 masks at all times.

Standard personal protective equipment includes N-95 masks, gloves, gowns, caps, and face shields or goggles [26, 27]. All staff should be mask fit-tested to ensure adequate seal. When performing high-risk procedures such as intubation, bag-mask ventilation, or bronchoscopy, protection should be enhanced with powered air-purifying respirators. Also, the HCW should be aware that these procedures have been associated with increased risk of infection transmission and should upgrade to airborne infection control precautions [28] (Table 34.1).

In view of the high risk of disease transmission during endotracheal intubation, airway management protocols have been proposed: Early intubation should be

Table 34.1 Standard personal protective equipment

Facial respirator (EU FFP2 or US NIOSH certified as N-95)
Eye protection (goggles or a face shield)
Clean nonsterile, long-sleeved gown
Gloves (some procedures required sterile gloves)
Procedures performed in an adequately ventilated room (>12 air changes per hour)
Avoidance of unnecessary individuals into the room
Attention to hand hygiene before and after patient contact and after removing personal protective equipment

performed, preferably in the ICU, rather than performing a crash intubation on the ward. Adequate sedation and neuromuscular blockade is recommended during intubation to minimize cough and dispersion of respiratory secretions. Finally, the procedure should be performed by the most experienced person available to minimize the dispersal of infectious particles and reduce the number of individuals exposed during intubation [29]. Measures to minimize respiratory droplet transmission include using in-line suctioning to maintain the ventilator circuit as a closed system. Humidification should be done via heat-moisture exchangers with viral-bacterial filter properties rather than heated humidifiers. Each ventilator should have two filters—one between the inspiratory port and ventilator circuit and the other between the expiratory port and ventilator circuit—to provide additional protection from exhaust gases and minimize ventilator contamination [26].

Other general recommendations include using a unidirectional/displacement ventilation system for a single patient room. It should *not* be used in a multi-bed ward where the potentially aerosol-transmitted infection patient source is unknown as this ventilation system may unintentionally disseminate the infection throughout the ward to other patients. Hence, the situation where such a ventilation system is used needs to be considered carefully. Even though an ideal isolation unit is fitted with a negative-pressure system and sliding glass doors (to reduce airflow generated by traditional hinged doors), it is possibly the movement of people in and out of the room that produces the most significant airflow. Of course, it is impossible to prevent such movement in a health care facility, but reducing the number of times the room is entered or exited can reduce the volume of potentially infected air exchanged across the doorway.

An essential component of an infection-control strategy is staff training. Clear management protocols must implemented, including the use of PPE, monitoring staff health, quarantining staff, transport of patients, transfer to the ICU, airway management, aerosol generating procedures, environment and equipment disinfection, and visitation policies.

The health care environment could be an important reservoir for viruses, bacteria, and fungi during outbreaks, given their proven ability to survive on surfaces and to become airborne. Changes in temperature and humidity in hospitals could have relevance for the viability of microorganisms and their spread to other patients. Adequate ventilation is necessary to dilute the airborne microbial load. Heat and humidity need to be controlled. It is recommended that upper and lower limits for temperature and humidity be specified according to the outbreak

pathogen and that air changes at the patient level be tested regularly, especially after any restriction to airflow.

It is important for intensive care providers to be prepared to meet the challenge of large-scale airborne epidemics causing mass casualty respiratory failure. Previous outbreaks have exposed the vulnerability of HCWs and highlighted the importance of establishing stringent infection control and crisis management protocols. There should be an established lung-protective, low tidal volume strategy for treating patients with acute lung injury or ARDS who require mechanical ventilation. The use of NIV remains controversial. Current infection-control policies that limit or prohibit the use of NIV as a high-risk intervention are based largely on supposition [30]. Standard contact and airborne precautions should be instituted in the ICU, with special care taken when aerosol-generating procedures are performed (Table 34.2).

Table 34.2 Infection control strategic bundle in prevention of nosocomial transmission of swine-origin influenza virus (S-OIV) A(H1N1)

1. "Just-in-time" education of infection control practice to health care workers
(a) Open infection control forum for all staff and special session for various clinical departments
(b) Special session for staff who are attending isolation facilities
(c) Special session for staff when inpatients and coworkers are confirmed with S-OIV
2. Enhanced infection control practice
(a) Enforcement of standard and transmission-based precautions in clinical area, especially with directly observed hand hygiene practice
(b) Wearing surgical mask at all times in patient care area and compliance on cough etiquette
(c) Regular environmental cleaning with soap and water and ad hoc environment cleaning with disinfectant (sodium hypochlorite 500 ppm) upon identification of confirmed case of S-OIV
3. Early recognition of index case in hospitalized patients
(a) Triage of suspected patients in emergency room and admission to isolation facilities
(b) Alertness of patients with nosocomial onset of upper respiratory tract infection and referral to isolation facilities
(c) Implementation of rapid molecular diagnostic test with turnaround time within 24 h
4. Preventing introduction of index case to other hospitalized patients
(a) Promoting absenteeism for sick health care workers
(b) Giving 7-day sick leave for infected health care workers
(c) Visitors wearing a surgical mask in the hospital and promoting directly observed hand hygiene for visitors
5. Audit of infection control compliance
(a) Unobtrusive hand hygiene observation and monitoring the compliance of wearing surgical mask
(b) Monitoring the consumption of alcohol-based hand rub in the hospital
(c) Monitoring the incidence of nosocomial influenza A infection
6. Administrative support
(a) Provision of alcohol-based hand rub at every bed, all ward entrances, and corridors
(b) Provision of manpower and equipment for laboratory diagnostics and contact tracing
(c) Coordination of infection control training sessions for staff

Key Major Recommendations

- The evidence regarding the risk of transmission during NIV is conflicting and unclear.
- There have been reports of NIV being effective in treating patients during an epidemic, reducing the need for intubation.
- NIV should be used especially in a pandemic scenario when the demand for mechanical ventilation support is overwhelming.
- Health care workers performing NIV during an airborne epidemic should use standard, contact, and airborne protection, including respirators of N-95 standard or higher.

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Controlling Spread of Viruses and High-Risk Infections to Hospital Health Care Workers from NIV

35

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Keywords
Spreading • Virus • Health care workers • Hospital • Infections

35.1 Introduction

Noninvasive positive-pressure ventilation (NIV) has been used successfully to treat acute respiratory failure arising from various conditions such as chronic obstructive pulmonary disease exacerbations, acute pulmonary edema, and pneumonia in immunocompromised patients [1]. There are debates on whether NIV should be considered a high-risk procedure that can be safely used for patients with respiratory infections [2]. NIV has been used to treat patients with respiratory failure due to severe acute respiratory syndrome [3, 4] and human H5N1 influenza infections [5, 6]. Spread of these infections to health care workers (HCWs) was reported [7]. The risk of such spread has been summarized in a systemic review, which estimated that the risk of transmission of infection from patients to HCWs from NIV are elevated with a pooled odds ratio of 3.1 (95 % confidence interval 1.4–6.8) from two studies in the review [8].

The question, then, is whether modifications of the environment (e.g., general and local exhaust ventilation) and improvements in NIV technology could improve the safety of using NIV in patients with respiratory infections. This chapter first illustrates the importance of aerosol sizes in aerosol dispersion and then summarizes studies on aerosols from NIV in experimental and human studies. Environmental modifications are beyond the scope of this chapter.

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35.2 Transmission Mechanisms: Importance of Aerosol Size

Communicable respiratory disease may be transmitted through various routes, including direct and indirect contact, airborne transmission, and droplet transmission [9]. Airborne transmission has been well described in the health care setting for tuberculosis [10], chickenpox [11], and measles [12]. Debate continues, however, on whether other diseases are transmitted primarily by airborne or droplet routes.

The key to defining transmission of respiratory infections from patients to HCWs relates to the deposition of aerosols from patients by various physical mechanisms: inertial impaction, sedimentation, interception, electrostatic attraction, and diffusion [13]. Gravitational settling through sedimentation is most important for large particles, whereas diffusion is the main mechanism for small particle deposition. Very small particles take awhile to settle and thus remain airborne for a long time and can travel a longer distance before settling.

Particle deposition is influenced by two important factors: the size of the particulates and their velocity. These factors could be related to the amount of aerosol generated by the patient or from the ongoing respiratory procedure. There is no exact particle size cutoff at which pathogen transmission changes from exclusively droplet to airborne, or vice versa, although the World Health Organization [14] and the U.S. Centers for Disease Control and Prevention [15] both use a 5-μm cutoff to distinguish between airborne (≤5 μm) and droplet (>5 μm) transmission. Rather, as the size of particles decrease to a certain smaller size, droplet transmission presumable blends into airborne transmission [9].

When inhaled, large particles with aerodynamic diameter (AED) >25 μm are removed in the upper airway through impaction in the nasopharyngeal region, and either ejection by blowing of the nose or ingestion into the gastrointestinal tract by swallowing. Small particles (1–20 μm AED) are deposited in the tracheobronchial area. They are usually removed from the lung within a few hours by the mucociliary escalator and thus have limited residence time in the lung. Very small particles (<10 μm AED) have a better chance of penetrating the terminal bronchioles and alveolar sacs [16].

35.3 Aerosol Dispersion Distance

35.3.1 Mathematical Modeling: Wells' Evaporation–Falling Curve

An important issue regarding aerosol dispersion relates to their evaporation after they are expelled from the patient's respiratory tract. Using mathematical modeling and making references to the Wells evaporation-falling curve of droplets [17], Xie et al. [18] estimated that large droplets (60–100 μm diameter) could totally evaporate before falling to the ground at 2 m from the source of emission. Also, a high velocity of expulsion (e.g., by sneezing) could carry these droplets a longer distance from the source. Environmental factors, such as relative humidity and temperature,

would affect the rate of droplet evaporation and thus the ultimate distance to where the droplets would settle.

35.3.2 Experimental Studies on Aerosol Dispersion Distances from NIV

Studies have been published regarding the size of aerosols from patients with respiratory infections [19] and aerosol dispersion derived from various respiratory procedures, such as use of oxygen through a simple oxygen mask [20, 21] or jet neubilizers [22]. Only a few studies focused on the aerosol dispersion from the use of NIV.

In an experimental setting, Hui et al. [23] studied the dispersion of oil-based smoke particles emitted from a manikin NIV model. The smoke particles were <1 μm in diameter and were visualized by a thin laser light sheet and digital image capturing. Various levels of inspiratory positive airway pressure (IPAP) (10–18 cmH_2O) and a constant expiratory positive airway pressure (EPAP) (4 cmH_2O) were applied. It was found that at IPAP 18 cmH_2O, a jet plume from the exhaust hole could extend to 0.45 m above the patient with horizontal spread along the ward ceiling. The authors concluded that substantial exposure to the NIV exhaust could occur within a 0.5 m radius of patients undergoing NIV.

35.3.3 Effects of Using Different IPAP Pressures on Aerosol Dispersion

Hui et al. [23] also found that higher IPAPs were associated with longer aerosol dispersion distances from the NIV mask. A turbulent jet flow was created that reached a vertical distance of 0.4–0.45 m above the mask when the IPAP was increased from 10 to 18 cmH_2O. The dispersion distance decreased to 0.25 m at IPAP 10 cmH_2O when nasal bridge leakage was present.

35.3.4 Effects of Different NIV Mask and Exhalation Devices on Aerosol Dispersion

Use of different NIV masks and exhalation devices affect the dispersion of aerosols. In another setting, Hui et al. [24] studied oil-based smoke particulate dispersion distances through two mask and exhalation devices: (1) Respironics ComfortFull 2 full-face mask with built-in exhalation diffusers and (2) Respironics Image 3 full-face mask with an external Whispering Swivel exhalation port. It was found that the Image 3-Whispering Swivel exhalation port had higher maximum dispersion distances at all the tested IPAPs: 0.95 m at IPAP 10 cmH_2O; >0.95 m at IPAP 14 cmH_2O and 18 cmH_2O. The corresponding dispersion distances for the Comfort Full 2 mask were 0.65, 0.65, and 0.85 m at IPAP 10, 14, and 18 cmH_2O, respectively. The

diffusion from the Image 3-Whispering Swivel combination was also more diffuse and extensive. The difference in dispersion distance could be related to the design of the mask and the exhalation port.

35.3.5 Limitations of Experimental Studies

There are several limitations in the experimental studies using smoke particles. The measured smoke particles in the studies of Hui et al. are <1 μm, which are not typical of aerosol sizes generated from real patients. Detection of the dispersed smoke particles by laser and digital photography is supposed to be accurate, but the sensitivity of such methods have not been addressed by the authors. Real-life environmental factors, such as evaporation of aerosols and the effects of the room, have also not been considered.

35.3.6 Human Study Results on Aerosol Dispersion from NIV

Only one human study regarding aerosol dispersion from NIV could be identified at the time of this writing. Simonds et al. [25] recruited three groups of participants (normal subjects, subjects with coryzal symptoms, and subjects with chronic lung disease exacerbations). They underwent respiratory therapy including chest physiotherapy, oxygen therapy, nebulized medications, and NIV. Measurements of aerosol sizes and number were made at two positions, one immediately adjacent to the participants (D1) and the second position at 1 m from the participants (D2). The authors found that treatment with NIV using standard circuits significantly increased the amount of aerosols >10 μm at position D1 for subjects with chronic lung disease and for coryzal subjects. At position D2, coryzal subjects generated significantly more aerosols of sizes 3–5 and 5–10 μm, and there was a borderline significant increase in aerosols at >10 μm (Fig. 35.1).

35.3.7 Effects of Circuit Modifications on Aerosol Dispersion in Human Study

In the same human study, Simonds et al. [25] modified the NIV circuit by adding a viral/bacterial filter between the mask and the exhalation port. They found that there was no significant increase in the amount of aerosols of any size at either position (D1 or D2), suggesting that addition of a viral/bacterial filter to the circuit might reduce the generation of aerosols >10 μm. The change in air pressure inside the breathing circuit or the patient's effort in respiration was not measured after adding the viral/bacterial filter, but the authors commented that its use did not seem to increase the work of breathing.

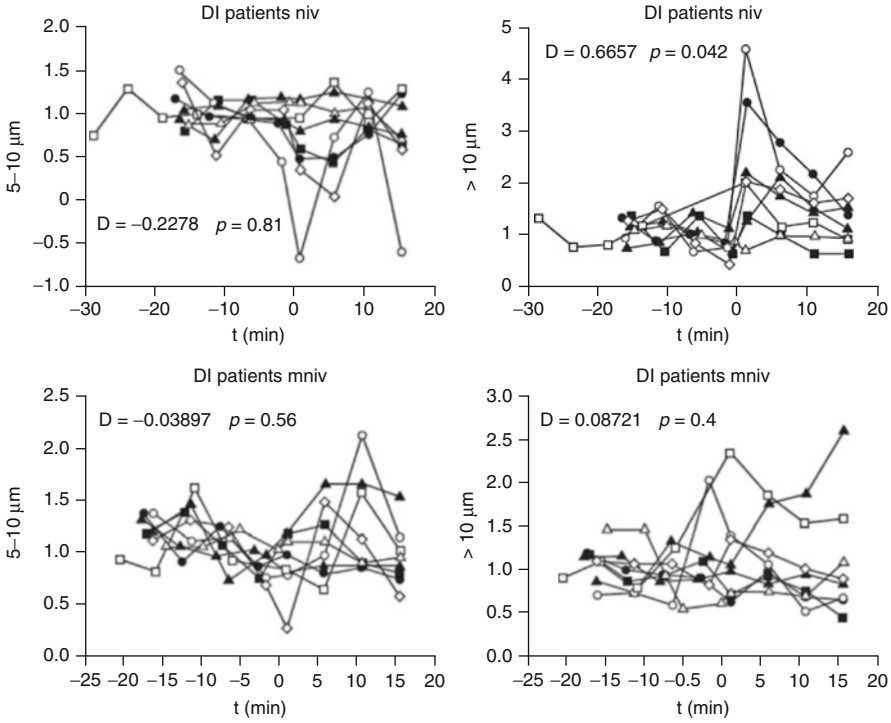

Fig. 35.1 Non-invasive ventilation circuit (NIV) (top row) and modified NIV results (bottom row) in patients at D1 in ranges 5–10 µm and >10 µm. Adopted from [25]. Reprint with permission

35.4 Implications for Control Measures

Experimental studies using small smoke particles (<1 µm) suggest that their dispersion is within a 1-m range. Dispersion of the smoke particles appears to be more widespread when the Whispering Swivel is used as the exhalation port. On the other hand, it is observed from patient studies that the use of NIV with a vented mask generates predominantly large droplets (>10 µm), and their deposition in the environment is mostly within a distance of 1 m from the patient. Addition of a viral/bacterial filter in the NIV circuit appears to be effective in decreasing the number of large dispersed aerosols. Dispersion of smaller droplets (<10 µm) does not increase after the use of NIV in normal subjects or patients with coryza or chronic lung disease exacerbations.

35.5 Conclusion: Balance Between Efficacy and Risk

The use of NIV for lung infections should be a balance between its potential usefulness and its potential nosocomial transmission of the pathogen. Uncertainties always arise in the clinical setting when clinicians are facing patients with pulmonary infiltrates and acute respiratory failure but have not identified the pathogen causing the problem. Given such uncertainty and in the face of possible unknown emerging infections in the future, perhaps the precautionary principle [26] should be adopted: "When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically."

Key Major Recommendations

- These findings have important clinical implications.
- Firstly, there are very few studies, both experimental and human studies, that address the aerosol dispersion problem of NIV, and cautious interpretation of these limited results is advised.
- Secondly, use of full personal protective equipment, including the use of effective respiratory protection, should be enforced for health care providers who are working within a 1 m of the patient treated with NIV because of the increase in large aerosols within this distance.
- Thirdly, infection control measures, such as handwashing and surface decontamination of the surrounding environment, should be observed to decrease the spread of infection through fomites and other direct contact with the environment.
- Lastly, if NIV is chosen for use in patients with suspected communicable respiratory diseases, special consideration to the breathing circuit setup should be made. Specifically, the choice of exhalation device would be of concern. Also, the use of viral/bacterial filters on the circuit, if they do not significantly increase the work of breathing for the patient, might be considered because they could help decrease the amount of large aerosols.

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Part VI

Hospital Organization: Department Organizations

Noninvasive Ventilation in Patients with Infectious Diseases in the Emergency Room

36

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Keywords
Non invasive ventilation • Emergency room • Pandemic Influenza

36.1 Introduction

Noninvasive ventilation (NIV) has a lower complication rate than orotracheal intubation and is better tolerated by patients [1]. NIV constitutes an efficient intervention in patients with cardiogenic edema and chronic obstructive pulmonary disease (COPD), and is necessary in carefully selected patients with shortness of breath and hypoxemia [1, 3, 4]. Phua et al. [5] examined the efficacy of the NIV in patients with hypercapnic respiration and reported a mortality rate of 32 %.

The utilization of NIV in patients with shortness of breath due to hypoxemia has shown good results, producing improved oxygenation, reduced fatigue, and reduced mortality while avoiding the complications of orotracheal intubation. However, a number of reports have questioned NIV use in patients with infectious diseases [1, 2].

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Table 36.1 Arterial blood gases values in COPD patients in the emergency room

COPD + CAP	Parameter	Initial pH	pH after 1 h	Initial PaO_2	PaO_2 after 1 h
GOLD 2	IPAP 10 cmH_2O EPAP 4 cmH_2O	7.31	7.38	52 mmHg	56 mmHg
GOLD 3	IPAP 12 cmH_2O EPAP 4 cmH_2O	7.29	7.36	48 mmHg	52 mmHg

COPD chronic obstructive pulmonary disease, *IPAP* inspiratory positive airway pressure, *EPAP* expiratory positive airway pressure

36.2 Is the NIV the First Option in Infectious Disease Patients?

Treating patients with NIV who have an infectious disease is controversial. For those with a community-acquired pneumonia (CAP), early application of NIV reduces the risk of requiring orotracheal intubation, days in the hospital, and the riskof infections associated with mechanical ventilation. Confalonieri et al. [3] evaluated the efficacy of NIV in 56 patients with pneumonia, observing a significant decrease in the days in hospital and increased survival. Ferrer et al. [1] reported lower rates of intubation, septic shock, and mortality after 90 days in patients with severe pneumonia who underwent NIV.

36.3 NIV During the Influenza A(H1N1) Pandemic

When NIV was not applied as the first line of management for respiratory failure in patients with hypoxemia caused by influenza A(H1N1), the failure rate was over 80 %. In the United States and Canada, the initial guidelines did not recommend the use of NIV because of wanting to protect health care professionals [8].

Domínguez et al. [8] reported their experience with mechanical ventilation during the influenza pandemic in Mexico. In our hospital, NIV was a successful intervention in 91 patients with pneumonia and advanced COPD, preventing intubation in 63 (69 %). In a group of diabetic patients with influenza, NIV prevented intubation in 52 % (Table 36.1).

Belenguer et al. showed that NIV improved oxygenation by gasometry in patients recently admitted to the intensive care unit (ICU) [6, 7]. More recently, a Spanish group reported the benefits of early NIV in influenza patients [9]. In the emergency room (ER) at our institution, we experienced a 30 % success rate (37/234) among patients with respiratory failure.

36.4 NIV and the Immunodeficient Patient

Another group of patients who frequently require NIV upon arriving at the ER are immunodeficient patients with serious pulmonary infections caused by opportunistic agents. We also applied NIV to patients with hematological illness, preventing

the use of intubation in 44 % of the patients. This group can be benefited by the use of NIV, presumably with a reduced incidence of nosocomial infections. However, most of the studies providing data were published during the 1990s and were case reports. At present, most inmunodeficient patients treated with NIV are human immunodeficiency virus-positive. They have shown improvement with the application of continuous positive air pressure and have had a reduction in mortality due to *Pneumocystis jirovecii* pneumonia [10].

36.5 Safety of Health Care Professionals

Although NIV can create a significant risk of spreading infectious disease to health care professionals, this risk can be addressed by use of a number of safety measures. These measures include application of standard and respiratory precautions for all personnel and visitors to the area, including airborne and droplet transmission precautions. Regular training and supervision of personnel for donning and doffing is paramount to the safety of the health care workers, particularly during outbreaks. Similarly, visitors accessing infectious areas should be thoroughly supervised to ensure that they exercise all precautions during their stay in the area.

Key Major Recommendations

- Non invasive ventilation has a lower complication rate than orotracheal intubation
- Is well tolerate by patients
- Has a relevant paper in a respiratory pandemic

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Noninvasive Mechanical Ventilation in Patients with High-Risk Infections in Intermediate Respiratory Care Units and on the Pneumology Ward

37

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Keywords
Pneumonia • COPD • Ventilator equipment • Caregiver

37.1 Introduction

Several studies have examined the benefit of noninvasive ventilation (NIV) as first-line therapy in some critically ill patients versus conventional therapy [1]. Currently, NIV is frequently started outside the intensive care unit (ICU)—not only in the emergency department but also in general wards with less-extensive monitoring facilities [2, 3]. Plant et al. [4] showed that it is possible to apply NIV to patients with chronic obstructive pulmonary disease (COPD) and hypercapnic acute respiratory failure (ARF) in the general ward provided the respiratory failure is not severe (assessed by pH > 7.30). A European survey of a European Respiratory Society Task Force [5] defined the ICU as a location with a high staff-to-patients ratio and facilities for performing invasive ventilation and monitoring. It defined a respiratory intermediate ICU (RIICU), or a high-dependency unit, as a specific clinical area that has the capability of performing continuous vital sign monitoring and a staff-to-patient ratio somewhere between those for an ICU and a general ward

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(usually 1:4). Clinical criteria for performing NIV in an RIICU are based on mental status and the presence (or absence) of multi-organ failure [1].

The increased risk of pneumonia attributable to endotracheal intubation (ETI) has stimulated the use of alternative tools to deliver positive-pressure ventilation. The use of NIV is associated with lower rates of nosocomial infection, so its use should be encouraged whenever appropriate [6]. Nevertheless, a document endorsed by the European Respiratory Society and the European Society of Intensive Care Medicine stated that NIV should not be considered an alternative to ETI for ARF secondary to infection with the H1N1 virus that is worsening to become acute respiratory distress syndrome (ARDS) [7]. According to this document, however, NIV can be considered to prevent further deterioration and avoid the need for ETI in patients with mild to moderate hypercapnic or hypoxemic ARF and/or distress due to cardiogenic pulmonary edema in the absence of pneumonia, multiple organ failure, and/or refractory hypoxemia. It can be also used to prevent postextubation respiratory failure in patients with improving ARDS secondary to H1N1 infection, preferentially when the patient is no longer contaminated. These warnings are even more important when considering the potential use of NIV for ARF due to high-risk infections outside the ICU.

37.2 Patients

Despite the fact that specific randomized studies are lacking, severely ill patients should be treated immediately in the ICU [1]. Hypercapnic COPD patients with ARF due to infection can be treated in the general ward provided isolation is not necessary and the staff has adequate expertise [7]. In these cases, minimum monitoring includes regular assessment of the respiratory, hemodynamic, and neurological functions by adequately trained personnel 24 h a day [4]. In contrast, severely hypoxemic ARF should be treated at least in an RIICU, where monitoring and prompt ETI are available, thereby avoiding dangerous delays to appropriate treatment. In other words, the selection of patients must take into account the location where NIV is performed.

37.3 Equipment

Several studies have analyzed the acute use of NIV for respiratory infections in hospitals. They showed a lower infection rate for patients on acute NIV compared to those on invasive or conventional ventilation [8]. Risk factors for these patients on NIV include the ventilator, humidifier, and their circuits. Specifically designed NIV ventilators are used on general wards and in RIICUs. They often have only one tube from the ventilator to the patient, with an exhalation valve to the external environment. On the one hand this design means a lower risk of ventilator contamination because there is no airflow from the patient back into the ventilator. On the other hand, there is an increased risk of environmental and caregiver airborne

contamination. Studies have confirmed that nurses and physicians providing NIV and chest physiotherapy, working in contact with an infected patient, should have a higher level of respiratory protection [9]. Reports have demonstrated that the use of various facial masks for NIV is associated with substantial exposure to exhaled air leaking within 1 m from the patient. This risk varies according to the type of mask and is greater with increasing leakage and with higher inspiratory pressures [10].

Conclusion

There is limited knowledge about the role of the location outside the ICU (or RIICU) for NIV management of ARF due to high-risk infections. The patient's clinical status, location, and available equipment must be carefully evaluated before discharging him or her from the safety of the ICU. On the other end, during an era of resource restriction the choice of a less safe environment for NIV treatment might be considered "better than nothing."

Key Major Recommendations

- The use of NIV should be encouraged whenever appropriate because it is associated with lower rates of nosocomial infection.
- Noninvasive ventilation should not be considered an alternative to ETI for patients with ARF secondary to H1N1 infection.
- Hypercapnic COPD patients with ARF due to infection can be treated in the general ward provided isolation is not necessary and the staff has adequate expertise.
- Hypoxemic ARF should be treated at least in an RIICU where monitoring and immediate endotracheal intubation are available to avoid dangerous delays in care.
- Risk factors for patients in NIV include the ventilator, the humidifier, and their circuits.

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Organization of a Noninvasive Mechanical Ventilation Unit for Immunocompromised Patients

38

Jose Luis Sandoval Gutierrez, Lilian Reveles Zavala, Miriam Barrales Lopez, and Edgar Sevilla-Reyes

38.1 Introduction

At present, noninvasive ventilation (NIV) is widely used both in hospital and nonhospital settings [1]. In the hospital, the areas where NIV is acceptable are the intensive care unit (ICU), intermediate therapy areas, recovery room, emergency room, and wards.

More than 30 million individuals are infected with the human immunodeficiency virus (HIV), with respiratory diseases as a significant cause of their hospitalization [4, 5]. Immunocompromised patients have become a challenge in respiratory clinical care. Traditionally, they were not considered for NIV, but because of the availability of novel technologies and interfaces, more respiratory care is available for this group of patients [2].

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38.2 Possible Scenarios for the Immunocompromised Patient

Patients with particular diseases or in certain situations may be categorized as immunocompromised [3].

- After transplantation
- Hemato-oncological disease
- Acquired immunodeficiency syndrome (AIDS)
- Rheumatological disease
- Rheumatological disease with immunosuppressive treatment

38.3 Contraindications for the NIV

Noninvasive ventilation is contraindicated in a number of circumstances [5].

- Central nervous system alteration
- Hemodynamic instability
- Organic dysfunction
- Chronic hypoxemia
- Airway obstruction
- Recent facial surgery
- Gastroesophageal surgery
- Pneumothorax
- Vomiting

38.4 Hospital Resources Required for NIV Application

If NIV is to be undertaken in a hospital, that institution must meet certain criteria [6].

- There must trained professionals able to provide NIV.
- NIV and trained professional health care workers must be available 24 h a day.
- There must be prompt access to endotracheal intubation and conventional mechanical ventilation.
- Monitoring equipment and staff must be available.

Although NIV is not indicated for all patients, many can benefit from it. Based on the understanding of the facility, each hospital determines the best plan of action for NIV treatment of immunodeficient patients. Identifying the cause of a patient's respiratory failure is paramount for evaluating the suitability of NIV intervention. It must be clearly understood whether it is being applied therapeutically or as palliative care. It is necessary to evaluate prognostic scores using tools such as the Sepsis-Related Organ Failure Assessment (SOFA), Acute Physiology, Age, and Chronic Health Evaluation II (APACHE II), and the Simplified Acute Physiology Score II (SAPS II). The latter is applied in HIV-positive patients [7, 8].

38.5 Personnel Responsible for the NIV

The clinical team involved in NIV should include medical doctors, nurses, physical therapists, and other support personnel with knowledge, understanding, and acceptance in various areas.

- Understanding respiratory physiology
- Understanding and accepting the need for NIV
- Knowledge of possible complications
- Understanding the benefits of NIV

The working team may include medical doctors without respiratory specialization but with expertise in other specialties (e.g., infectious diseases, oncology, hemato-oncology, rheumatology).

38.6 Training

Theoretical and practical courses and their completion are required. These courses should include technical and clinical knowledge of devices, circuits, and interfaces. It is necessary to create a flowchart that outlines clinical care and evaluates it via a checklist. It should become well known and in use in all relevant hospital areas.

38.7 Monitoring of the NIV

There are some key aspects of monitoring the patient during NIV intervention.

- Patient status/evolution
- Physiological situation
- Ventilator parameters
- Interface data
- Patient–ventilator synchronization

38.8 Administrative Participation

Beyond the ICU and the ward, it is highly beneficial that administrative personnel know about the benefits of NVI so the quality of care is maintained. The following personnel should be kept well informed.

- Head of the area of the hospital that is involved in NIV care
- Heads of multidisciplinary participating departments: ICU, emergency room, nursing, auxiliary services and facility maintenance
- Head of respiratory therapy

Hospital norms regarding storage of material, levels of room isolation, maintenance, and cleaning are also important to maintain the quality of care required.

It is necessary to understand and consider that the quality of NIV care diminishes in areas outside the ICU. It occurs because there is a reduction in the nurse/patient ratio, less precise monitoring, and less decisive capacity in the presence of complications.

Noninvasive ventilation represents a great novel opportunity to treat and provide palliative care for respiratory pathologies in the immunocompromised patient, providing time for adequate communication between medical personnel and the patient's relatives regarding prognosis [9]. The growing acceptance of and familiarization with NIV among clinicians will present new opportunities and challenges for care of the immunocompromised patient [10].

Key Major Recommendations

- Patient selection is crucial.
- The ventilatory mode chosen–continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), proportional assist ventilation (PAV)—must be appropriate for the patient.
- The interface (facial, nasal, oronasal) must be chosen carefully, always with the individual patient in mind.
- Synchronization of breathing between the patient and the mask is sometimes difficult.
- Monitoring must be careful and adequate to avoid catastrophes.

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Pandemic Influenza Management and Control Policies: Hospital Coordination During an Influenza Pandemic

39

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Keywords
Pandemic influenza • Management • Hospital control

39.1 Introduction

Since its initial outbreak in April 2009, the pandemic H1N1 virus has posed a challenge to health systems around the world, compelling them to make available the benefits of scientific and medical progress to the entire population. Some of the most significant demands were access to early diagnostics, vaccines, and antiviral treatments as well as the responsiveness of hospital care, particularly in seriously ill patients who required attention in intensive care units (ICUs). The increased demand of medical care during an influenza pandemic is a heavy burden for any health system as it is added to the regular demand for heath care, which should not become paralyzed [1].

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39.2 Importance of Intensive Care Units

During the pandemic of influenza A(H1N1), as happened during the severe acute respiratory syndrome (SARS) outbreaks, ICU availability was necessary to save lives. The ICU should have the following staff and equipment available [2].

- Medical staff trained in intensive care 24 h a day, 7 days a week
- Inhalation therapy staff
- Biomedical engineering personnel
- Highly trained nursing staff for critically ill patients
- Sufficient, adequate modern technical equipment

Pandemic influenza is an infectious disease, so it is important to develop strategies to reduce the risk of infection within hospitals. The institutional response should focus on the following areas.

- Institutional Influenza Committee
- Supplies
- Capability of providing sufficient medical care
- Available care in ICUs
- Clinical care available for health care workers (HCWs)
- Prevention of nosocomial infections and their transmission to others
- Motivation of HCWs

Standardized protocols for managing the critically ill patient alone are not enough to provide quality care. It is the combination of all the aforementioned factors that would provide an environment for quality care.

39.3 Committees

The Institutional Influenza Committee (IIC) should coordinate efforts from all hospital departments involved in the clinical care of influenza patients. The IIC is composed of representatives from all of the departments involved: medical, nursing, administration, clinical laboratories, support services, teaching, physical security, and social communication.

The IIC can take the steps necessary to ensure quality of care in the ICU and other wards and departments using the most up-to-date practices. It evaluates the local experiences but also reaches out to other institutions at national and international levels. The flow of information during the twenty-first century is a tool that the IIC should understand and avail.

The IIC should also strengthen the implementation of standard precautions for prevention of nosocomial infections. Under the standard practices model, everyone in the hospital setting should be considered both potentially infectious and susceptible to infection. For example, during procedures that form aerosols (endotracheal intubation, fibrobronchoscopy, aspiration, noninvasive mechanical ventilation) HCWs should have sufficient protocols, training, and materials to protect themselves and protect patients and others while providing quality care. The IIC should be directly involved in creating such an environment and should develop the tools to evaluate compliance to protocols and performance of these operations.

The IIC should also consider psychological counseling for health personnel involved in the operation along with regular communications with all the institutional personnel in the form of posters, memoranda, and short briefings. The Communication Department can help with this task.

During committee meetings, the IIC must analyze the current information and arrive at clear resolutions while avoiding cathartic discussions. The latter, if deemed necessary, should take place only under strict psychological supervision.

39.4 Hospital Organization

To protect patients, personnel, and visitors, it is necessary to strengthen surveillance and restrict access and patient flow in the hospital. At the entrance of consultation services, monitoring stations consisting of medical or paramedical personnel with gel sanitizer and respiratory masks must be in place to question arriving patients or visitors about the presence of fever and/or respiratory symptoms.

In the emergency room, it is necessary to have a separate access point and waiting room for patients with respiratory symptoms. There should also be a dedicated triage area for filling out a questionnaire, assessing vital signs, and pulse oximetry.

Influenza patient should be hospitalized in an area separated from the rest of the patient population. Health personnel should not rotate to other services because this practice provides better care to the patients and reduces the risk of other workers being exposed to the virus.

When the demand for care and hospitalization increases, rational use of hospital resources must be ensured. As half of the patients are young with little serious coexisting disease, elective surgery and nonurgent procedures should be postponed. Also, supplies of key items for treating influenza patients (e.g., drugs, medical devices, supplies for prevention, clinical laboratory tests, radioimaging) should take priority.

Avoid overcrowding and reduce contact between staff members. It is not advisable for health personnel to concentrate in poorly ventilated areas or in crowds. Information sessions can be conducted in classrooms or large rooms for necessary briefings.

39.5 Personnel Management

Overall, the workload for the average employee serving hospital patients increases during an epidemic. There are increased numbers of patients on mechanical ventilation and seriously ill patients who require more care and generate more tension as they offer contagion risk. At the same time, there is a rise in emergency room patients along with a lower number of workers due to illness or disability or to decreased attendance associated with an individual's decision to avoid exposure.

A key part of a hospital's response is the provision of information to all staff on all shifts. Such information should be given with common sense and making the HCWs feel that they are important to the institution and are part of the responsibility and commitment of the authorities. It is also important to ensure break shifts where

the worker can leave the hospital, with no liability related to the management of the epidemic. Such measures can help avoid the "burn-out" syndrome [3].

39.6 Patient Discharge

Patients are discharged after improvement, transfer, or death. For each of these situations, it is indispensable to prepare all of medical and paramedical logistics to facilitate the situation. For example, many patients require supplemental oxygen, which should be provided and connected to the patient before discharge. Pulmonary rehabilitation programs also should be scheduled before discharge.

A critical care ambulance with trained staff is required for most patient transfers. The institution should verify that the ambulance has all the human and material resources. In case of death, the Pathology Department staff must be notified so they can take appropriate actions regarding safe management of the body and use personal protective equipment themselves.

39.7 Handling of Protocols

At the start of an epidemic, standardized care protocols for handling cases should be published by the Ministry of Health (in countries that have one) and hospital authorities. Other organizations, such as professional associations, may also publish their own recommendations. It is important to reach a consensus practice as it is desirable that health personnel in charge adhere as much as possible to what their health system agreed were the optimum conditions for their system.

During a pandemic, recommendations may change, and doses, procedures, and therapeutic indications may be constantly revised. One example was the use of noninvasive ventilation (NIV) during a human pandemic, which initially was contraindicated because of the risk of contagion, aerosolization, and the risk to health care personnel [4]. In retrospect, NIV benefited patients who were subjected to it in the form of noninvasive mechanical ventilation or intubation not authorized by the patient [5]. A similar experience was reported in the SARS epidemic [6].

Key Major Recommendations

- A triage system is mandatory in pandemic influenza.
- Non invasive ventilation is a major resource in the pandemic.
- Psychological counseling.
- Influenza committee in necessary.
- Supplies.

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Part VII

Guidelines and Protocols

Noninvasive Mechanical Ventilation Guidelines and Standard Protocols for Noninvasive Mechanical Ventilation in Patients with High-Risk Infections

40

Stefanie Keymel and Stephan Steiner

Keywords
NIV • Guidelines • High-risk infection

40.1 Introduction

Noninvasive ventilation (NIV) is associated with lower rates of endotracheal intubation and decreased mortality in patients with acute respiratory failure. Therefore, NIV should be preferred to invasive ventilation whenever possible [1]. In clinical settings, most of the patients were treated by NIV because of pulmonary edema or exacerbated chronic obstructive lung disease (COPD) [2]. With endemic and high-risk infection, most of the critically ill patients develop acute lung injury (ALI) and/or acute respiratory distress syndrome (ARDS). Furthermore, NIV, an "aerosol-producing factor" might be regarded as a high-risk procedure for medical staff [3].

We discuss two issues here: guidelines and protocols for NIV and specific recommendations regarding its use during endemic infections, especially in high-risk infections such as severe acute respiratory syndrome (SARS) or influenza (H1N1 virus).

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Table 40.1 Indications for the use of NIV based on the current guidelines

Indications for NIV [9]	Mode
Palliative care in patients not considered for intubation	NIV
Acute exacerbated COPD with hypercapnic failure	NIV
Cardiogenic pulmonary edema	CPAP, NIV
Hypercapnic respiratory failure due to chest wall deformity or neuromuscular disease	CPAP, NIV
Weaning and postextubation failure	CPAP, NIV
RF in immunocompromised patients	CPAP, NIV
Improvement of ventilation during bronchoscopy	CPAP, NIV

NIV is not generally recommended for the use in acute respiratory failure due to acute respiratory distress syndrome or acute lung injury
RF respiratory failure, *CPAP* continuous positive airway pressure, *NIV* noninvasive ventilation, *COPD* chronic obstructive pulmonary disease

40.2 Guidelines and Protocol for NIV in the Acute Care Setting

As a result of the growing importance of NIV in emergency and intensive care medicine, several guidelines on this topic were published during the last decade. The following overview summarizes the recommendations on NIV in patients with ALI and ARDS, which are known to complicate high–risk infections.

In 2001, an international expert group concluded that NIV may substitute for invasive ventilatory support in patients with hypoxemic respiratory failure due to pneumonia. The authors noted that there were only three randomized studies comparing NIV with invasive ventilation and that they had different endpoints and results [2]. A year later, the British Thoracic Society (BTS) published guidelines on the use of NIV in patients with acute respiratory failure (ARF). They did not consider the treatment of ALI due to respiratory infection. Conversely, at this time severe hypoxemia was regarded as a contraindication for NIV [4]. Certainly, there was no link to high-risk infection at that time. The Canadian Critical Care Trials group made no recommendations about the use of NIV in ARDS patients or those with severe community-acquired pneumonia (CAP) in 2011 [5]. In summary, compared to NIV for exacerbated COPD (hypercapnic respiratory failure), cardiogenic lung edema, or postextubation failure, the data regarding the use of NIV in patients with hypoxemic ARF are less clear [1].

40.2.1 Indication for NIV

Tables 40.1 and 40.2 summarize common accepted indications and contraindications for NIV. NIV might be considered in patients with tachypnea and a respiratory rate >24 breaths/min, a poor alveolar gas exchange level as indicated by $PaO_2/FiO_2 < 200$ mmHg, and/or severe dyspnea accompanied by the use of accessory respiratory muscles [6]. Beyond this, NIV may be undertaken as a therapeutic trial with a view to tracheal intubation if it fails or as a ceiling of treatment in patients who are not candidates for intubation [4]. It should be emphasized that intubation

Table 40.2 Contraindications for the use of NIV [2, 9]

Cardiac or respiratory arrest
Severe encephalopathy
Severe upper gastrointestinal bleeding
Facial surgery/trauma
Inability to cooperate/protect the airway
High risk for aspiration

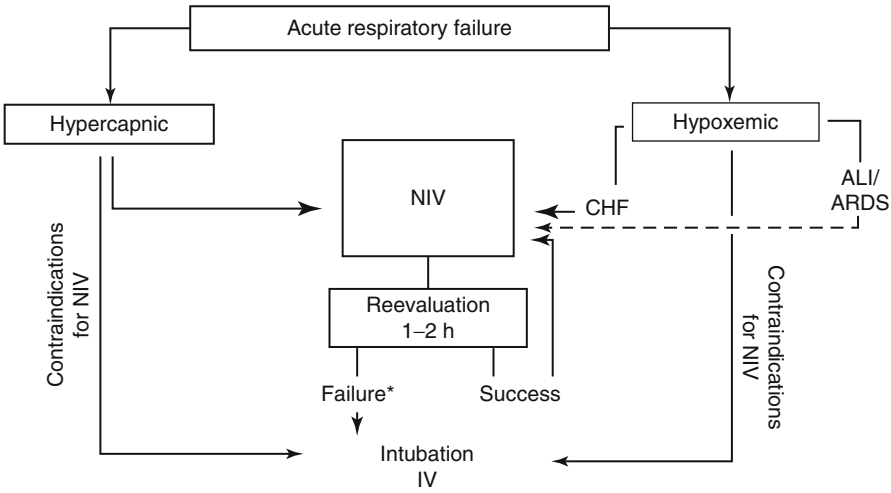

Fig. 40.1 Noninvasive ventilation (*NIV*) in patients with acute respiratory failure. There is a strong recommendation for NIV in those with hypercapnic respiratory failure and hypoxemic failure associated to cardiogenic edema. None of the guidelines favor NIV in patients with acute lung injury or acute respiratory distress syndrome because of lack of evidence. If NIV is used in these patients, early detection of failed NIV requires careful monitoring. *Signs of NIV failure: worsening of gas exchange, hemodynamic instability, change of mental status, signs of respiratory fatigue. See Table 40.2 for contraindications

should be performed early in patients with pneumonia and ARDS who do worsen or have not improved after 1–2 h [7, 8] (Fig. 40.1).

40.2.2 Protocol and Practical Approach to NIV

There is a broad agreement that NIV should be conducted in the intensive care unit (ICU), where immediate expertise is available to enable a rapid transition to invasive ventilation if needed [1, 8, 9].

40.2.3 Choice of Interface

Noninvasive ventilation is defined as ventilator assistance to the lungs without an artificial airway. There are various devices, including negative-pressure ventilators

(e.g., the so-called tank ventilator, or "iron lung"), several masks, and helmets. Because of limited practicability, tank ventilators do not play a major role in modern intensive care medicine. Selection of the optimal interface—which connects the ventilator to the nose, mouth, or both—is an essential part of NIV. Air leakage, discomfort, or claustrophobia might result in patient intolerance. In the acute care setting, nasal, oronasal, or full-face masks are primarily used [1, 4, 5]. There are few randomized controlled trials comparing the use of an oronasal mask with a nasal mask. Nevertheless, the oronasal mask has been better tolerated than nasal mask or full-face mask [1, 10]. Because there is a lack of evidence regarding which interface is best, some guidelines do not give recommendations about the use of interfaces [5]. Others favor the use of a full-face mask for the first 24 h, switching to a nose mask if preferred by the patient [4, 11].

In general, masks and exhalation valves that are licensed as reusable by the manufacturer require high-level disinfection. They should be disassembled in their parts and then undergo an automatic process using washer, disinfector, and dryer.

Attaching a bacterial filter to the ventilator's output can minimize respirator contamination [4]. As an alternative, using single-use material could reduce the risk of infection.

40.2.4 Mode of NIV

Noninvasive ventilation can be performed using pressure support ventilation, proportional assist ventilation, or volume-controlled ventilation [1, 2]. Schönhofer et al. [1] recommended the use of positive-pressure ventilation with inspiratory pressure support and positive end-expiratory pressure (PEEP). As patients with ARF are often agitated and have pronounced respiratory drive, ventilation triggered by the patient's own respiratory efforts is beneficial compared to controlled, time-based ventilation. When there is not sufficient spontaneous inspiratory effort or it is inadequate to trigger the ventilator, pressure-controlled ventilation could be used [1, 2]. Other guidelines do not emphasize a mode of ventilation on the strength of insufficient evidence [5]. Similar to invasive ventilation, ventilator settings should be adjusted to provide the lowest inspiratory pressures or volumes needed to improve oxygenation and patient comfort, which can be estimated by the decrease in the respiratory rate and respiratory muscle unloading [2]. Because most of the critical ill patients with SARS or H1N1 virus infection develop ARDS and ALI, a lung-protective ventilatory strategy and fluid restriction are essential.

40.2.5 Clinical Course and NIV Failure

The most important parameters during the clinical course are $PaCO_2$ (arterial partial pressure of carbon dioxide), pH, respiratory rate, dyspnea, and alertness. The aforementioned parameters have to show a trend toward improvement during the first 2 h of NIV [1]. The NIV failure rate in patients with hypoxic respiratory failure is

estimated to be 30 % (CAP) to 50 % (ARDS) [7, 9, 12]. Failure occurs early or after a few days [1]. It should be noted that NIV failure is associated with a worse outcome, which might be a consequence of a delayed response to the NIV failure because of inadequate monitoring or delayed definitive care [13]. Other predictors of failure are the duration of NIV, oxygenation index, and the Simplified Acute Physiology Score II at admission, and, as expected, the length of ICU stay [7]. Other authors found a high APACHE score, copious respiratory secretions, poor nutritional status, and confusion or impaired consciousness to be associated with NIV failure [2].

40.3 Specific Recommendations for Using NIV in Patients with Endemic and High-Risk Infections

There are specific problems concerning the use of NIV in patients with endemic and high-risk infections. First, there are no controlled trials on this topic. Therefore, recommendations are largely based on supposition [3]. It is of concern that NIV, as an "aerosol-producing procedure," possibly increases the risk of caregiver exposure or of exposure to other patients, which would be disastrous in case of a pandemic. Therefore, organizations such as the World Health Organization [14] and the UK National Health Services Agency [15] published guidelines that treat NIV as a high-risk procedure. Nevertheless, there are no controlled data comparing particle dispersion between individuals undergoing NIV and those who are not. Furthermore, it should be kept in mind that endotracheal intubation also is at risk of transmitting disease.

In an experimental model, Hui and coworkers [16] found that flow from a noninvasive ventilator may increase occupational risk. As this risk may be mediated by air leaks, fitting the mask properly is essential. Full-face masks and helmets might be superior to nasal masks.

Also, NIV must be managed under strict isolation measures with adequate protection (e.g., N-95 mask) of the health care workers who attend to the patients. As far as possible, infected patients should be isolated in rooms with negative pressure.

Although most of the guidelines do not recommended use of NIV, it has become part of the standard treatment protocol for SARS [17]. Han et al. [18] demonstrated that NIV was not only effective in avoiding intubation and invasive ventilation, it effectively reduced the ICU length of stay. No infection was detected in 155 health care workers, and their serology tests for coronavirus were negative.

Key Major Recommendations

- Current guidelines do not recommend NIV for the treatment of hypoxemic respiratory failure in endemic and pandemic infections (e.g., SARS or H1N1). However, the level of evidence is low.
- Noninvasive ventilation appears to be a reasonable option in carefully selected cases, which should be treated under optimal conditions with awareness of NIV failure and might be regarded as a high risk procedure for medical staff.

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Guidelines for Health Organizations: European Perspectives and Experience in Pandemics

41

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Keywords
Pandemics • Noninvasive ventilation • European recommendations

41.1 Introduction

In Europe, the rate of noninvasive ventilation (NIV) use in intensive care units (ICUs) is about 35 % for ventilated patients and higher (roughly 60 %) in respiratory ICUs or emergency departments. In North America, this form of ventilation is begun most often in emergency departments (EDs), most patients being transferred to the ICU or step-down units in hospitals with such facilities. This low rate of use in some hospitals is related to scarce knowledge on or experience with this technique, insufficient technical equipment, and inadequate funding. Despite these limitations, NIV is increasingly being used outside traditional and respiratory ICUs, including EDs, postsurgical recovery rooms, cardiology, neurology, and oncology wards, and palliative care units.

41.2 Analysis

Approximately 10–30 % of hospitalized patients with H1N1 virus infection require admission to the ICU (where available). Critically ill patients include those suffering from rapidly progressive lower respiratory tract disease, respiratory failure, and acute respiratory distress syndrome (ARDS) with refractory hypoxemia [1].

Before the severe acute respiratory syndrome (SARS) outbreak in 2003, there was no evidence to support the idea that the use of NIV might increase the risk of

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infectious disease transmission. Despite the paucity of epidemiological data, the idea that NIV leads to increased occupational risk has gained currency. In fact, some organizations such as the Canadian Diseases Advisory Committee have published recommendations to avoid NIV in patients with febrile respiratory illness [2]. Other studies show that NIV can be used effectively and safely in such situations by applying strict infection-control procedures [3–5].

The European Society of Intensive Medicine and the European Respiratory Society guidelines recommend when NIV should be considered (or not) after reviewing studies following the last H1N1 pandemics in Europe [6]: NIV must not be considered in patients with severe hypoxemic acute respiratory failure (ARF), rapid development of ARDS, or multiorgan failure. Invasive ventilation is recommended for these patients. NIV may be considered to prevent further deterioration and intubation needs in patients with mild-to-moderate hypercapnic ARF due to cardiogenic pulmonary edema or exacerbation of a chronic respiratory disease secondary to H1N1 infection in the absence of pneumonia, multi-organ failure (MOF), or refractory hypoxemia. It can also be used to prevent postextubation respiratory failure in patients with resolving ARDS secondary to H1N1 infection, preferably when patients are no longer contaminated.

There is growing concern about droplet dispersion during NIV, but it is important to note that similar exposures may occur during routine oxygen therapy by mask, coughing or sneezing, or procedures such as bronchoscopy and aerosol delivery.

Recommendations for droplets include patient isolation with protective measures for health care providers and other patients, use of double-circuit tubes and special filters for nonrebreathing devices, minimization of leaks, preferably full-face mask or helmet interfaces, avoidance of heated humidifiers, and disposing of mask and tubes after use according to routine infection control procedures [7].

The Spanish Society of Intensive Care Medicine, after collecting data from its hospital network, developed a document with recommendations for the management of severe complications in the H1N1 flu pandemic [8]. The document states that:

> …noninvasive mechanical ventilation cannot be considered a technique of choice in patients with acute respiratory distress syndrome, but could be useful in experienced centers and in cases of respiratory failure associated with exacerbation of chronic obstructive pulmonary disease or heart failure. It can be used in highly experienced centers, with appropriate helmet-type interfaces and patients who have reported very good results, although only in a few cases.

The use of NIV and its risks have been discussed in many documents. In 2009, the Scottish government published a guide on NIV in pandemic flu patients. The recommendations on NIV are somewhat complex, but they ultimately suggested that NIV could be used effectively and safely in such situations under strict infection-control procedures. These conclusions were reached in the United Kingdom are shown in Table 41.1 [9]. The recommended equipment and materials are shown in Table 41.2.

In some circumstances, a continual leak of unfiltered gas from the exhalatory circuit may be anticipated, and consideration should be given to adopting a policy

Table 41.1 Conclusions of guidance on infection control for critical care and NIV of Scottish Government and Health Protection Scotland

Staff should be trained in infection control.
Gown, gloves, and eye protection should be worn for all aerosol-generating procedures. The use of an FFP3 respirator instead of a surgical mask may be advisable until there are data that allow better assessment of the risk associated with the various procedures.
Patients should be managed in negative-pressure single rooms with anterooms, where this condition is available. If such facilities are not available, the patients should be cared for in standard single rooms or, if there is no other option, in cohorted groups.
A nonvented patient mask or helmet should be used.
Although bilevel pressure support (BiPAP) NIV is likely to be preferred, CPAP ventilation may be used in certain circumstances. A high-efficiency bacterial/viral breathing system filter (BS EN 13328-1) should be used between the nonvented mask and the expiratory port and at the outlet of the ventilator.
Expiratory port options include a whisper swivel or controlled leak valve (each with a proximal filter, as above). Ideally, expiratory flow should be directed through a single jet away from patients and staff.
NIV masks should be applied to the patient's face and secured before the ventilator is turned on.
Double-tube circuit ventilators may be advantageous.
The ventilator should be turned off before removing the close-fitting mask or when lifting the mask away from the face (e.g., for mouth care or fluid sips).
Water humidification should be avoided.

Table 41.2 Recommended equipment and material for infection control in critical care patients

Disposable patient respiratory equipment must be used wherever possible.
Reusable equipment must be decontaminated in accordance with local policy and the manufacturer's guidelines.
Closed systems should be used wherever possible (e.g., suction).
All respiratory equipment used on patients, including transport ventilator circuits and manual resuscitation aids, should include a high-efficiency bacterial/viral breathing system filter (BS EN 13328-1).
Breathing filters should be changed in accordance with the manufacturer's guidelines.
The ventilatory circuit should not be broken unless absolutely necessary.
Staff should be alert regarding power supply due to unplanned breathing circuit disruption: (1) Breathing circuits should be checked regularly for tightness of fit in component parts. (2) Caution is necessary when moving or performing other care on ventilated patients to minimize the risk of accidental disconnection.
For planned circuit breaks, appropriate PPE and FFP3 respirators should be worn as for aerosol-generating procedures.
Procedures for the rapid deployment and use of appropriate PPE and FFP3 respirators in the event of an unplanned breathing circuit disruption should be developed and rehearsed.

for the staff working close to the patient of wearing FFP3 respirators and eye protection for extended periods throughout a shift. Examples of leaks of unfiltered gas include: (1) situations where no bacterial/viral filters are available and therefore

ventilator circuits have to be used unfiltered and (2) when high-frequency oscillatory ventilators are used.

The World Health Organization recommends special considerations in NIV-treated patients, including additional precautions in EDs and ICUs [10].

- Noninvasive ventilation [bilevel positive airway pressure (BiPAP), continuous positive airway pressure (CPAP)]: standard and droplet precautions unless indicated otherwise by new evidence of increased transmission risk.
- Nebulization: standard and droplet precautions. Nebulizer treatment should be performed in an area that is physically separated from other patients (e.g., treatment room, screened enclosure).

In relation to supportive therapies for hypoxemia treatment, oxygen support is recommended but with no distinction between invasive and noninvasive ventilation, except in lung-protective ventilation strategies [1].

Regarding NIV in pandemics, Italian and French guidelines refer to the World Health Organization or the Centers for Disease Control and Prevention for its implementation, without further information.

Conclusions

The currently suggested best practice for NIV delivery in patients with pandemic flu pneumonia in Europe are summarized in Table 41.1. After a revision of the necessary organization and infrastructures in case of a pandemic, the following conclusion was drawn: Each hospital bed must dispose of its oxygen supply and suction, especially in areas involving expected NIV use [11].

Key Major Recommendations

- Noninvasive mechanical ventilation cannot be considered a technique of choice in patients with ARDS but could be useful in experienced centers and in cases of respiratory failure associated with exacerbation of chronic obstructive pulmonary disease or heart failure.
- It is preferable to perform NIV using an appropriate helmet-type interface.
- Concerning droplet dispersion during NIV, similar exposures may occur during routine oxygen therapy by mask or procedures such as bronchoscopy and aerosol delivery.
- Water humidification should be avoided.
- All respiratory equipment used on patients, including transport ventilator circuits and manual resuscitation aids, should include a high-efficiency bacterial/viral breathing system filter (BS EN 13328-1).

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Noninvasive Mechanical Ventilation in Patients with High-Risk Infections: Current and Future Perspectives

42

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Keywords
Non-invasive mechanical ventilation • High risk infections • Health care workers
Aerosol transmission

42.1 Introduction

Noninvasive ventilation (NIV) is currently an essential component in the management of acute respiratory failure (ARF) in the emergency department and the intensive care unit (ICU) [1]. During the 1950s, the widespread use of the iron lung during the polio epidemic increased the survival rate of patients with respiratory failure [2, 3]. Although the use of NIV has increased and the number of articles on NIV has increased rapidly over the past decades [3–5], there are still insufficient data concerning the applicability of NIV in patients with ARF due to pulmonary infections, such as H1N1, severe acute respiratory syndrome (SARS), tuberculosis, and other infectious agents. NIV had been used in patients with SARS in the 2002–2003 outbreaks and during the H1N1 influenza epidemic in 2009. In recent years, the use of NIV has been extended to patients with respiratory failure due to a wide spectrum of infectious diseases. They include but are not limited to the SARS and avian influenza (H5N1) pandemic.

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However, some concerns have been raised with the use of NIV in patients with contagious diseases. Studies from Mexico, Canada, Spain, and Australia have reported experiences with the use of NIV for respiratory failure due to H1N1 influenza [5, 6]. Although significant proportions of these patients were treated with NIV, there were no published reports of disease transmission from patients to health care workers (HCWs) with the use of NIV. It must be stated, however, that involved HCWs were not routinely screened for infections. Nevertheless, the World Health Organization has included NIV among aerosol-generating procedures for which the risk of pathogen transmission is possible [7, 15]. At the individual level, interventions to reduce transmission include the use of face masks and other physical barriers when administering NIV.

Currently and as a general clinical conclusion, the use of NIV can avert or reverse respiratory failure and therefore decrease the rate of endotracheal intubation (ETI) in a elected group of infectious patients. Although only few reports of infectious disease transmission with NIV therapy have been published, reasonable and adequate precautionary steps should be taken to protect HCWs as well as other patients and family members.

Although there are various studies on the protection of HCWs from patients using facemasks and respirators for influenza, SARS, and tuberculosis, we recommend that further research be done to determine whether currently proposed NIV protocols prove effective in reducing infectious particle dispersion and spreading of disease to others.

The evidence regarding the use of NIV in patients with ARF from pandemic agents is mainly derived from experience gained from the recent SARS outbreak and the H1N1 pandemic. The published evidence consists of observational case series and case reports only, which are graded as “weak” following the GRADE working group criteria. Bearing this limitation in mind, the authors make the following recommendations.

42.2 NIV Indications and Results in Pandemic ARF

The use of NIV has changed the treatment of mechanical ventilation in patients with ARF. Observational studies recommend that NIV may be used to treat severe pneumonia such as seen in H1N1 infection, SARS, and tuberculosis. In a Toronto study, a number of HCWs contracted SARS when a patient was intubated following NIV failure. NIV was then discouraged for such patients [7]. Two subsequent observational studies from China found no evidence of viral spread to HCWs who took appropriate precautions. NIV was also used in the treatment of ARF due to H1N1. In a Chinese study, 23 of 64 patients were ventilated initially with NIV. Only three of them were intubated [8, 9]. In a Spanish study, NIV had a 50 % failure rate. In the event of pandemic, ventilator resources are likely to be severely strained, and NIV may offer comfort to some of the afflicted [10].

The use of NIV may have reduced morbidity in patients with ARF from the pandemic by avoiding intubation. When allocating the limited number of ICU beds and

ventilators during public health emergencies, NIV may provide an alternative to IMV in some patients. Selection of patients for a trial of NIV must comply with general recommendations and contraindications for using NIV. In particular, because of reports of high NIV failure rates in H1N1 patients with ARF, NIV should not be seen as the ultimate therapy. The patients should be monitored for signs of NIV failure. NIV should be applied by only experienced teams and in appropriately monitored settings such that failure of NIV can be readily recognized and promptly followed by invasive mechanical ventilation.

42.3 NIV and Risk of Aerosol Transmission to HCWs

Aerosol transmission of infectious disease occurred between infected and uninfected ferrets separated by U-bend and S-bend tubes 2.5 m in length and connected only by an airstream comparable to that of human breathing. These transmission models and theoretical examples highly suggest that aerosol transmission of influenza is plausible [11]. There are no reports of increased risk of transmission of infectious agents during the use of NIV, but no studies used systematic screening or used a case–control methodology. Also, there are limited data on the use of masks and respirators to induce transmission of infectious disease.

Bin-Reza et al. [12] suggested that mask use is best undertaken as part of a package of HCW protection, especially together with hand hygiene. The effectiveness of facemasks and respirators is likely linked to early, consistent, and correct usage. The authors, however, considered that the risk for airborne transmission should not preclude the use of NIV in appropriately selected patients, provided that precautions are taken to limit this risk. Some consider that NIV is contraindicated in patients with ARF due to a respiratory airborne disease unless it is used inside a negative-pressure isolation room.

It has been shown that NIV produces droplets of 10 mm. Because of their large mass, most of these droplets fall onto a surface within 1 m of the patient [13]. During a human sneeze, approximately 40,000 particles 0.5–12.0 μm in diameter are released at 100 m/s. Sneezed particles from shedding influenza patients most likely contain influenza virions. Infection control measures designed to limit aerosol spread may have less relevance than the "usual" measures of protection that even HCWs should adopt [14]. Evidence from laboratory studies of potential airborne spread of influenza from shedding patients indicates that guidelines are related to the current 1-m respiratory zone. A larger respiratory zone of airborne spread of infectious disease has implications for the protection of HCWs regarding ocular inoculation [15]. These precautions consist of (1) avoiding open outlets, (2) using bacterial, viral, and droplet filters in the ventilatory circuit, (3) applying personal barrier precautions (masks, goggles, gowns), and (4) patient airborne isolation measures.

It is important to remember that NIV is an intermittent application of respiratory support. The patients can generate larger amounts of aerosols during unsupported

Table 42.1 NIV in patients with high-risk infections, by EBM grade

Parameter	EBM grade and classification
NIV risk of aerosol transmission to HCWs[a]	
NIV-SARS	No evidence, or grade E
NIV-H1N1	No evidence, or grade E
NIV-TB	No evidence, or grade E
Technical recommendations for NIV applications[b]	
NIV-SARS	Grade 1C or 1D for all technical aspects
NIV-H1N1	Grade 1C or 1D for all technical aspects
NIV-TB	Grade 1C or 1D for all technical aspects
Efficacy of NIV[c]	
Gas exchange ARF	
NIV-SARS	Grade 2C (if early stage of ARF)
NIV-H1N1	Grade 2C (if early stage of ARF)
NIV-TB	Grade 1C
Rate of ETI requirement	
NIV-SARS	Grade 2C (if early stage of ARF)
NIV-H1N1	Grade 2C (if early stage of ARF)
NIV-TB	Grade 1C
Is NIV a safe recommendation for pandemics?[d]	
NIV-SARS	Grade 1C
NIV-H1N1	Grade 1C
NIV-TB	Grade 1C

EMB endomyocardial biopsy, *TB* tuberculosis
[a]EBM grading classification.
[b]Is NIV a risk for aerosol droplet generation?
[c]Evaluate these aspects: (a) Technical issues: the ventilator's circuit interface (full-face or total-face helmet). (b) Protocols.
[d]Can NIV avert or reverse respiratory failure (check gas exchange) and/or decrease the rate of ETI requirement in selected contagious patients?

intervals. Thus, respiratory care protocols should be developed in the ICUs. Respiratory care and NIV protocols should reflect these precautions for the use of NIV. Grading of evidence for NIV use during infectious epidemics and pandemics using the standard GRADE criteria is summarized in Table 42.1.

Key Major Recommendations

- The use of NIV can avert or reverse respiratory failure and therefore decraese rate of ETI in infections patients.
- The use of NIV may have reduced morbidity in patients with ARF from the pandemic by avoding intubation.
- Respiratory care protocols should be developed in the ICUs.

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