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GUIDELINE

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Guidelines for high-flow nasal cannula oxygen therapy in neonates (2022)

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Abstract

High-flow nasal cannula (HFNC) oxygen therapy, which is important in noninvasive respiratory support, is increasingly being used in critically ill neonates with respiratory failure because it is comfortable, easy to setup, and has a low incidence of nasal trauma. The advantages, indications, and risks of HFNC have been the focus of research in recent years, resulting in the development of the application. Based on current evidence, we developed guidelines for HFNC in neonates using the Grading of Recommendations Assessment, Development and Evaluation (GRADE). The guidelines were formulated after extensive consultations with neonatologists, respiratory therapists, nurse specialists, and evidence-based medicine experts. We have proposed 24 recommendations for 9 key questions. The guidelines aim to be a source of evidence and reference of HFNC oxygen therapy in clinical practice, and so that more neonates and their families will benefit from HFNC.

KEYWORDS
guidelines, high-flow, infant, newborn, nasal cannula, oxygen inhalation therapy

1 | INTRODUCTION

Respiratory failure is one of the main problems encountered in neonatal intensive care units (NICUs). The national and regional multicenter research conducted by the Chinese Collaborative Study Group for Neonatal Respiratory Diseases found that 13.2%—19.7% of patients admitted to NICUs were diagnosed as neonatal respiratory failure. Of these neonates with respiratory failure, the mortality ranged from 24.7% to 32.1%.[1,2] Nasal continuous positive airway pressure (NCPAP) ventilation is widely used as noninvasive respiratory support in neonatal respiratory failure. It plays an active role reducing neonatal mortality and the risk of bronchopulmonary dysplasia (BPD), and improving neurodevelopmental outcomes.[3,4] However, NCPAP requires experienced nurses, as an improper use may lead to nasal injuries such as ulceration, granulation, and vestibular stenosis. Additionally, wearing fixed nasal prongs may increase neonatal discomfort.[5,6]

High-flow nasal cannula (HFNC) oxygen therapy has been a popular type of noninvasive respiratory support, widely used in NICUs because it is comfortable, easy to setup, and has a low incidence of nasal trauma.[7–13] There is an increasing number of studies on the advantages, indications, and risks of using HFNC in neonates, as well as comparing its effectiveness with that of NCPAP and other noninvasive ventilation modes. However, uncertainty surrounding the use of HFNC in the NICU remains, and cultural differences in China regarding the preferences and values of Chinese parents bring up the necessity to develop HFNC guidelines that consider Chinese culture. The following guidelines are based on China's current situation, its NICUs status, resource utilization, Chinese families preferences, and current available evidence and expert advice. We proposed 24 recommendations for 9 key questions to standardize the clinical use of HFNC in neonates in China and reduce its risks, therefore increasing the number of neonates that will benefit from HFNC.

2 | METHODS

2.1 | Purpose

To aid clinical practitioners learn more about the advantages of HFNC, to standardize the use of HFNC, and to optimize the sequential treatment strategy of neonatal respiratory support.

2.2 | Target audience and recipients of interventions

These guidelines apply to all neonate and can be used by doctors, respiratory therapists, nurses, and anesthesiologists involved in neonatal clinical care.

2.3 | Guidelines initiation and formulation

These guidelines were initiated by the Evidence-Based Medicine Group, Neonatologist Society, and the Chinese Medical Doctor Association in February 2020, who later established the guidelines working group. Therefore, the members of the guidelines working group come from the Neonatologist Society, Chinese Medical Doctor Association. The latter has many years of clinical and research experience, and it was established by neonatologists, respiratory therapists, nurse specialists, anesthesiologists, and evidence-based medicine experts. The guidelines working group takes full account of authority and regionalism to ensure the representativeness in the guidelines of the regional development imbalance and economic differences.

The guidelines were formulated in nine stages: (1) understanding the existing guidelines in China and foreign countries, and formulating the implementation plan of the guidelines; (2) training on literature screening, evidence extraction, and evidence-based guidelines formulation strategy; (3) confirming the background, purpose, target population, and users of the guidelines, investigating, proposing, discussing, and formulating the clinical questions; (4) registering in the practice guidelines REgistration for transPAREncy (PREPARE); (5) searching, screening literature, and evidence extraction, synthesizing evidence and assessing the quality; (6) formulating recommendations and the first draft of the guidelines by the guidelines working group; (7) discussing and reviewing the guidelines through the external review experts and forming final recommendations; (8) finalize; and (9) feedback after publishing.

2.4 | Guidelines registration

This guidelines were registered in the practice guidelines Registration for transparency ((PREPARE) http://www.guidelines-registry.org) (no. IPGRP-2020CN042). These guidelines followed the *WHO Handbook for Guidelines Development*, 2nd ed, issued by the World Health Organization in 2014, with reference to the definition of clinical practice Guidelines proposed by the Institution of Medicine (IOM) in 2011, the *Basic Methods and Procedures for Developing/Revising Clinical Practice Guidelines* (Chinese Medical Association, 2016), *the Guidelines for Developing/Revising Clinical Practice Guidelines in China (2022 Edition)*, the Appraisal of Guidelines for Research & Evaluation II (AGREE II), and the Reporting Items for Practice Guidelines in Healthcare (RIGHT; http://right-statement.org).[14–18]

2.5 | Guidelines application environment

The application environment of this guidelines was NICUs, neonatal departments, delivery rooms, and transport in all medical units levels.

2.6 | Formulating questions

Based on a systematic literature search and clinical practice, and through the interviews of other interested parties like NICU medical staff and parents, primary questions were identified. Overall, 18 questions were formulated in PICO (population, intervention, control, and outcomes) format, and 9 key questions underwent two rounds of reviews by specialists, including indications, contraindications, parameter settings, and comparison with other noninvasive ventilation modes. The selection and grading of the outcome indicators was the responsibility of the guidelines development working group, as follows: 1—3 not important, 4—6 important, and 7—9 as critical for that outcome indicator.

2.7 | The guidelines working group

The guidelines working group consists of five working groups: (1) The guidelines steering committee comprised experienced neonatologists and evidence-based medicine experts, and provided management

support, drafted the framework, determined clinical problems, supervised the guidelines process, and managed conflicts of interest. (2) The guidelines development working group comprised neonatologists, neonatal respiratory therapists, nurse specialists, anesthesiologists, and methodology experts and were responsible for identifying clinical problems, overseeing the process of evidence retrieval and synthesis, grading of recommendations, assessment, development and evaluation (GRADE) rating, and formulating and determining the strength of the recommendations. (3) The guidelines evidence evaluation committee was responsible for evidence retrieval, literature screening, evidence extraction, and evidence synthesis. (4) The guidelines secretaries committee was responsible for arranging and coordinating meetings and collecting expert opinions. (5) The external review committee comprised neonatologists from the Neonatologist Society, Chinese Medical Doctor Association, and critical care specialists with senior experience, and was responsible for reviewing the guidelines and formulating the final recommendations. The editorial board of the Journal of Evidence-Based Medicine will be responsible for the final review of the guidelines.

2.8 | Conflicts of interest

All relevant guidelines development personnel declare no financial or nonfinancial conflicts of interest directly related to the guidelines, and we have all signed conflict-of-interests declarations.

2.9 | Evidence retrieval

The guideline would verify the available literature (in Chinese and English) related to the use of HFNC in neonates until June 1, 2022. The retrieved databases included PubMed, EBSCO, OVID, Web of Science, The Cochrane Library, CNKI, WanFang Data, and VIP Database. The references of relevant literature were traced as supplements. The MeSH terms in English are "infant, newborn," "oxygen inhalation therapy," "nasal cannula." The following search terms were used: "high flow," "HFNC," "high flow nasal cannula," "high-flow nasal cannula" "heated humidified high-flow nasal cannula," "humidified high flow nasal cannula" and other free terms. The retrieval mode was formulated according to the retrieval strategy of each database platform and was improved after pre-retrieval. Inclusion criteria were guidelines, expert consensus, systematic review/meta-analysis, randomized controlled trials (RCT), and observational studies. The exclusion criteria were as follows: full text not available, lack of references, translated guidelines, and studies with ineligible quality evaluation results. The document screening process is illustrated in Figure 1.

2.10 | Literature screening and evidence extraction

Two researchers independently screened the studies according to the inclusion and exclusion criteria. For the same clinical problem, when there were inconsistent results in meta-analyses, guidelines, expert consensus, and research results, these guidelines follow the principle of preferring the most recently published. If any new research is published, the guidelines working group will extract the original data and do a new meta-analysis to obtain the final evidence. When disagreement arose, joint consultation with third parties was done.

2.11 | Evidence synthesis

Evidence was obtained for each clinical question. If a high-quality systematic review was published in the last 5 years, it was used as evidence for the clinical problems. If there were no systematic reviews, or the systematic reviews presented no significant differences between them, evidence synthesis was performed based on the original studies included in the development or update of the systematic reviews. The AGREE II, Assessing the Methodological Quality of Systematic Reviews 2, Cochrane Risk of Bias Tool, and Newcastle-Ottawa Scale were used to evaluate literature quality. The evaluation process was performed independently by two members; disagreements were resolved by consensus or third-party consultation.

2.12 | Evidence quality

Based on relevant evidence, we used the GRADE to assess and grade the quality of the included evidence, with the GRADEpro and the Guideline Development Tool (GDT).[19,20] The quality of evidence was divided into four levels: high, moderate, low, and very low (Table 1). RCTs were initially classified as high-quality evidence; five factors reduced evidence quality (risk of bias, inconsistency, indirectness, imprecision, and publication bias). Observational studies (including cohort studies, cross-sectional studies, case reports, etc.) were initially classified as low-quality evidence, but three factors could increase evidence quality (large effect, possible confounding, and dose-response gradient). The recommended intensity was divided into two grades: strong and weak recommendations (Table 2).

2.13 | Formulating recommendations

Based on the evidence and expert opinions currently available, the guidelines development working group considered resource utilization, preferences of neonates and their families, fairness, and feasibility to formulate recommendations. The consensus was reached on each recommendation and recommendation strength, and finally 24 recommendations were established. Recommendation strength was graded according to the consensus level of the Delphi technique; items with support >70% were approved. Unapproved recommendations were revised by the development working group and included in the guidelines after reaching consensus.[21] For questions without direct evidence, or with only expert opinions from guidelines, the recommendations were formulated using the Delphi technique, and the strength

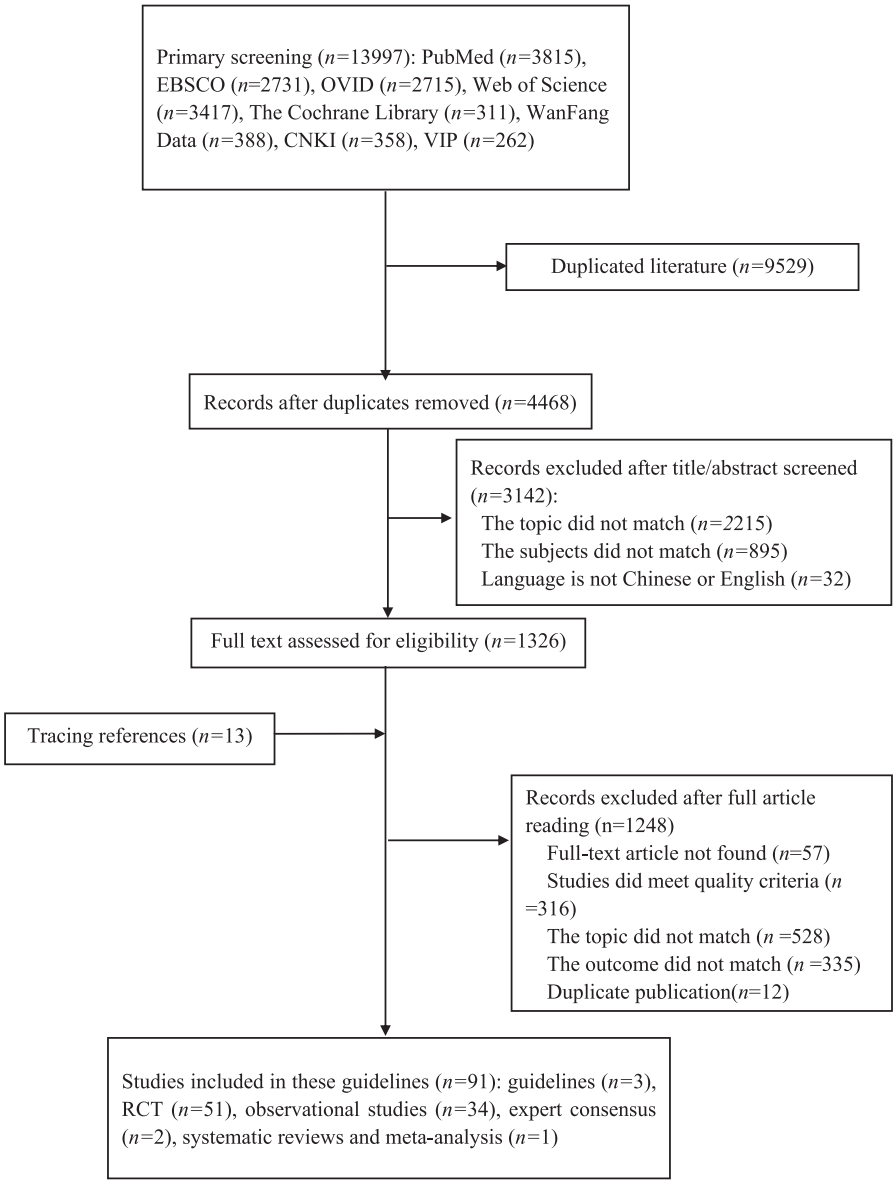

FIGURE 1 Studies selection process.

of evidence was set as a Good Practice Statement (GPS).[22] If no consensus was reached, such recommendation was not included in these guidelines. Since there was no direct original evidence related to some practical operation problems in clinical implementation, most are based on clinical experience or expert opinions. Implementing this GPS recommendation may bring great positive effects; therefore, it may be necessary for medical practice to use GPS recommendations.

2.14 | External review

The draft of the guidelines was reviewed by 14 external peer experts. Finally, the guidelines were revised and finalized according to 177 feedback comments.

2.15 | Dissemination and implementation

After the guidelines are published, they will be available in authoritative journals and other online sources such as WeChat and other network channels. They will be promoted within relevant academic conferences.

2.16 | Guidelines updates

These recommendations will be regularly updated as more evidence is collated and analyzed on a continuous basis, with major reviews and updates at least every 5 years. The next major update will be considered in 2027 by the guidelines working group.

TABLE 1 Quality of evidence in GRADE.

Grade	Definition
High (A)	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate (B)	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low (C)	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low (D)	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

TABLE 2 Recommendations and their strength.

Recommendation	Definition
Strong recommendation	Clearly shows the benefits of intervention outweigh the harms or more harms than benefits
Weak recommendation	Uncertain about the benefits and harms or the benefits and harms are tantamount regardless of the quality of evidence

2.17 | Guidelines publication

The guidelines will also be available in Chinese.

2.18 | Supplementary materials

The protocol of the guideline, the clinical question, the results of meta-analyses, results of GRADE, expert committee, results of the external review could be found online.

3 | HFNC EQUIPMENT AND MECHANISM

HFNC equipment delivers a heated and humidified flow with an oxygen concentration > 1 L/min (generally 2—8 L/min).[23,24] The equipment involves an air oxygen blender, which provides high-flow > 1 L/min (2–8 L/min) and can adjust the oxygen concentrations to 21%—100%; an active humidifier, which can effectively heat and humidify the respiratory flow; a respiratory circuit with a heating wire in the inspiratory limb (including an extension pipe without a heating wire) to help maintain and adjust the temperature and humidification of the flow; and nasal prongs with an aperture smaller than 1/2 of the nostril dimensions, which help reduce nasal trauma.[25]

3.1 | HFNC flow can provide positive end-expiratory pressure to maintain lung volume, which is positively correlated with flow. (D)

Unlike NCPAP, which sets and measures the flow or pressure to achieve the presets required for ventilation, HFNC uses flow without measuring the actual pressure.[26] HFNC can provide a low level of positive end-expiratory pressure (PEEP) to maintain lung volume.[27–29] Intrapharyngeal pressure (IPP), esophageal pressure (EP), and the effects of HFNC may not be different from those of NCPAP.[30,31] An observational study found no difference in EP between HFNC (4, 6, 8 L/min) and NCPAP (4, 6, 8 cmH_2O).[30] A prospective observational study using electrical impedance tomography found that HFNC flow (2–6 L/min) was as effective as NCPAP (5–8 cmH_2O) in maintaining the PEEP and ventilation distribution.[31]

The HFNC pressure usually increased with the increasing flow; however, it is affected by the opening and closing of the mouths of the neonates, resulting in pressure fluctuations.[27–29] The IPP increased with the increasing flow when the mouth was closed (IPP generated at the average flow rate of 1, 2, 3, 4, and 5 L/min was 1.70 ± 0.34, 1.75 ± 0.2, 2.62 ± 0.28, 3.78 ± 0.44, and 4.84 ± 0.51 cmH_2O, respectively).[27] End-expiratory esophageal pressure (EEEP), which is generally related to the intrapleural pressure, has been used as a surrogate for measurement of continuous distending pressures applied to the airways. EEEP was proportional to flow, $EEEP = 1.18 \times \text{flow}$, and was positively correlated with it. When the HFNC flow was 2—8 L/min, the corresponding EEEP range was 2—15 cmH_2O.[32] The pressure drop may have been caused by gas leakage when the mouth opens. In an in vitro study, in a closed model, the PEEP produced by HFNC increased linearly with an increase in flow. A flow of 8 L/min could provide PEEP up to 10 cmH_2O in term infants and 6 cmH_2O in preterm infants, where the pressure in the open model decreased by 50%.[33] When a neonate's mouth opens in a normal physiological state the clinical efficacy during HFNC may be reduced, but the excessive pressure generated in the closed state may lead to air pressure injury and/or hemodynamic changes. Therefore, improving clinical efficacy by routinely closing the mouth with a soother or others to increase the pressure is not recommended.

3.2 | HFNC flow flushes the dead space of the upper airway and improves gas exchange. (D)

High flow can flush dead space of the upper airway, especially in nasopharyngeal dead space, which helps eliminate carbon dioxide (CO_2) and improve gas exchange[34-36]; CO_2 removal is positively correlated with the flow.[33] With an increase in the HFNC flow, the arterial partial pressure of CO_2 gradually decreased; however, this correlation was not found with NCPAP. Therefore, an important role of HFNC treatment is to flush the nasopharyngeal anatomical dead space and remove CO_2 to maximize gas exchange efficiency.[37] An in vitro lung model study found that under closed-mouth conditions, the dead space CO_2 clearance time of HFNC was significantly shorter than that of

NCPAP ($p < 0.01$), and clearance efficiency increased with the increasing flow.[38] Because the proportion of the neonatal anatomical dead space (the dead space volume/tidal volume) is relatively large, the effect of improving the gas exchange by flushing the residual gas in the anatomical dead space is significantly effective.

3.3 | Heating and humidification of HFNC flow is beneficial in protecting airway mucosa. (GPS)

Under normal respiratory tract physiologic conditions, the nasal air passages warm and humidify the environment's air to 37°C and 100% relative humidity (RH).[35] However, the ciliary transport system of the neonatal respiratory tract is not mature yet, and inhalation of an unheated and dehumidified flow affects adversely the airway mucosa and ciliary functions, reducing lung compliance. Optimal heating and humidification can protect the airway mucosa and reduce metabolic work, complications, and extubation failure.[23] A randomized study in neonates found that the extubation failure rate of Vapotherm was lower than that of standard high-flow therapy (0% vs. 23.3%, $p < 0.01$).[39] It has been suggested that humidified and heated gas by HFNC is more beneficial.

3.4 | HFNC can reduce work of breath (WOB). (GPS)

HFNC provides flow at or above the peak inspiratory flow of neonates, which can reduce inspiratory resistance of the upper respiratory tract and reduce WOB.[35,40] Randomized and observational studies reported that HFNC can reduce WOB in neonates,[41,42] similar to NCPAP,[41,43–45] using respiratory induction plethysmography and monitoring diaphragm myoelectric activity.

4 | KEY QUESTIONS, RECOMMENDATIONS, EVIDENCE SUMMARY, AND RECOMMENDATION NOTES

4.1 | Question 1: What are the clinical indications for HFNC?

***Recommendation 1: HFNC can be used as an alternative to NCPAP for primary respiratory support of neonates with gestational age ≥ 28 weeks.* (2B)**

Evidence summary: Neonatal respiratory distress syndrome (NRDS) is a common, severe respiratory disease in preterm infants; pulmonary surfactant (PS) and noninvasive ventilation are important interventions. The systematic review/meta-analysis (27 RCTs, $n = 4250$) developed by the guidelines development working group found that the treatment failure rate (relative risk (RR) = 1.24, 95% confidence interval (CI) 0.94–1.62, $p = 0.12$) and mechanical ventilation rate (RR = 1.02, 95% CI 0.87–1.20, $p = 0.77$) had no significant difference when HFNC was compared to NCPAP for primary respiratory support after birth. Secondary outcome indicators included the incidence of air leak (RR = 0.60, 95% CI 0.43–0.82, $p = 0.001$), nasal trauma (RR = 0.40, 95% CI 0.33–0.49, $p < 0.00001$), and abdominal distension (RR = 0.49, 95% CI 0.29–0.83, $p = 0.008$), which were significantly lower in the HFNC group than in the NCPAP group. Additionally, the time to achieve full enteral feeding was earlier (standardized mean difference (SMD) = −0.38, 95% CI −0.67 to −0.09, $p = 0.01$) in the HFNC group. There was no difference in mechanical ventilation rates between the HFNC and NCPAP groups when other noninvasive ventilations were used as rescue therapy (RR = 0.99, 95% CI 0.52–1.88, $p = 0.97$).[46–72] Subgroup analyses of preterm infants with gestational age <28 weeks (two RCTs, $n = 38$) found no significant difference in intubation rate (RR = 0.43, 95% CI 0.15–1.24, $p = 0.12$) and BPD incidence (RR = 0.72, 95% CI 0.32–1.62, $p = 0.43$) between HFNC and NCPAP groups.[54,64]

Recommendation notes: This recommendation is based on available evidence. HFNC did not increase treatment failure or intubation rates when compared with NCPAP and has similar efficacy than that of NCPAP in primary respiratory support after the birth of neonates with a gestational age ≥28 weeks. Twenty-seven studies on neonates were included in the meta-analysis, among which two RCTs conducted subgroup analyses for extremely preterm infants (<28 weeks gestation), while two RCTs included full-term infants data. The subgroup analysis of extremely preterm infants found that although there was no significant difference in the incidence of intubation or BPD between the two groups; however, the sample size was small ($n = 38$). There is currently insufficient evidence for HFNC use in extremely preterm infants. It should be used with caution after assessing the clinical status of patients. Further analysis of these RCTs (three RCTs, $n = 1205$) found that a lower gestational age (<30 weeks) and higher inspired oxygen concentration ($FiO_2 > 30\%$) were associated with the HFNC failure rate ($p < 0.05$).[73–75] Other noninvasive respiratory supports such as NCPAP or nasal intermittent positive pressu ventilation (NIPPV) should be prepared while rescue therapy was required for the patients at high risk of HFNC treatment failure. Based on current evidence, the guidelines development working group recommends that neonates with a gestational age ≥28 weeks consider using HFNC as an alternative to NCPAP as primary noninvasive respiratory support.

Recommendation 2: HFNC can be used as an alternative to NCPAP for postextubation of neonates with gestational age ≥28 weeks. (2B)

Evidence summary: NCPAP is often used to reduce extubation failure after mechanical ventilation.[76] A systematic review/meta-analysis (12 RCTs, $n = 1606$) developed by the guidelines development working group showed that when comparing with NCPAP after extubation, there was no significant difference in the 72-h reintubation (RR = 1.24, 95% CI 0.78–1.97, $p = 0.37$) and mortality rates (RR = 0.72, 95% CI 0.43–1.18, $p = 0.19$), although the HFNC failure rate was higher (RR = 1.47, 95% CI 1.16–1.86, $p = 0.002$). Additionally, HFNC reduced the incidence of air leak (RR = 0.17, 95% CI 0.08–0.39, $p < 0.0001$), nasal trauma (RR = 0.35, 95% CI 0.27–0.47, $p < 0.00001$), and necrotizing enterocolitis (NEC) (RR = 0.47, 95% CI 0.26–0.84, $p = 0.01$). There were no statistically significant differences in the incidence

of other secondary outcomes, including complication rates such as BPD (RR = 0.91, 95% CI 0.70–1.18, $p = 0.46$), patent ductus arteriosus (PDA) (RR = 0.90, 95% CI 0.65–1.24, $p = 0.51$), retinopathy of prematurity (ROP) (RR = 0.83, 95% CI 0.54–1.27, $p = 0.40$), and intraventricular hemorrhage (IVH) (grade III-IV) (RR = 0.75, 95% CI 0.41–1.39, $p = 0.36$), hospital stay (SMD = −0.05, 95% CI −0.22 to 0.12, $p = 0.55$), oxygen therapy time (SMD = −0.02, 95% CI −0.15 to 0.12, $p = 0.79$), and the time to reach full enteral feeding (SMD = 0.20, 95% CI −0.22 to 0.63, $p = 0.35$).[50,62,65,72,77–84]

Recommendation notes: The 2016 American Academy of Pediatrics (AAP) clinical report on noninvasive respiratory support recommended HFNC as an effective alternative to NCPAP after extubation.[85] The 2019 European NRDS guidelines recommend that during weaning, HFNC can be used as an alternative to CPAP for neonates, with the advantage of less nasal trauma.[86] Among the 12 RCTs included in the meta-analysis, one of the treatment failure criteria for HFNC in a study protocol (fraction of inspired oxygen (FiO_2) > 30%) was lower than the treatment failure criteria (FiO_2 > 40%–60%) of other study protocols, which might increase the HFNC treatment failure rate. Additionally, more studies (eight RCTs) included extremely preterm infants, which may have expanded the treatment failure rate in the overall neonatal population. Based on the available evidence that HFNC and NCPAP have similar rates of reintubation and mortality in neonatal respiratory support after extubation, the guidelines development working group recommend that HFNC can be used as an alternative to NCPAP for postextubation of neonates with gestational age ≥28 weeks. If it fails, other noninvasive respiratory supports should be used as rescue therapy to avoid intubation where possible.

Recommendation 3: HFNC can be used as an alternative to NCPAP for the treatment of apnea in preterm infants with gestational age ≥ 28 weeks. (2D)

Evidence summary: Three studies were included in this recommendation, including one guideline,[87] one expert consensus,[88] and one observational study.[89] The "Evidence Support and Guidelines for Using Heated, Humidified, High-Flow Nasal Cannula in Neonatology: Oxford Nasal High-Flow Therapy Meeting" (*Oxford HFNC Guidelines*) suggest that HFNC can be used instead of NCPAP.[87] Indications for HFNC included apnea of prematurity (AOP) according to expert consensus in China.[88] An observational study ($n = 40$, corrected gestational age: 26.5–34 weeks) comparing HFNC and NCPAP for AOP found no significant difference in the frequency and duration of apnea, bradycardia, or desaturation per recording ($p > 0.05$).[89]

Recommendation notes: This item is recommended based on existing guidelines, clinical experience, and expert consensus, considering the feasibility of implementation, medical costs, and the comfort of neonates. Observational studies found that HFNC can reduce WOB similar to NCPAP.[41–45] Additionally, the physiological effects achieved during HFNC and NCPAP treatment are similar, including SpO_2, heart rate (HR), and FiO_2.[90–91] This suggests that it reduces upper airway and alveolar collapse, increases functional residual capacity, and reduces WOB through the low positive airway pressure generated by HFNC, thereby improving oxygenation and reducing the occurrence of bradycardia. For the treatment of AOP, HFNC had similar efficacy when compared with NCPAP. Although this study included extremely preterm infants at < 28 weeks gestation, the total sample size ($n = 40$) was small, and neonates were critically ill with rapidly changing conditions. Thus, it is necessary to evaluate the clinical status of neonates and to use it with caution. Therefore, these guidelines do not recommend HFNC as the first-choice treatment for AOP in extremely preterm infants. HFNC can be used for AOP in preterm infants at ≥28 weeks of gestation, but the overall quality of evidence is low. High-quality RCTs are required to provide evidence.

Recommendation 4: HFNC can be used as an alternative to NCPAP for noninvasive ventilation after INSURE strategy for preterm infants with gestational age ≥ 28 weeks. (2C)

Evidence summary: The intubation-surfactant-extubation (INSURE) strategy is effective for RDS treatment. The systematic review and meta-analysis (three RCTs, $n = 205$) developed by the guidelines development group compared the difference between the use of HFNC and NCPAP after the INSURE strategy in preterm infants. It was found that the incidence of nasal trauma (RR = 0.41, 95% CI 0.26–0.64, $p < 0.0001$) and air leak (RR = 0.26, 95% CI 0.08–0.89, $p = 0.03$) were significantly lower in the HFNC group than that in the NCPAP group. In addition, the 72 h reintubation rate showed no difference between these two groups (RR = 1.40, 95% CI 0.83–2.37, $p = 0.21$). The HFNC group did not increase the incidence of other complications, including BPD (RR = 0.89, 95% CI 0.49–1.61, $p = 0.70$), NEC (RR = 0.56, 95% CI 0.15–2.17, $p = 0.41$), ROP (RR = 0.95, 95% CI 0.52–1.75, $p = 0.87$), and IVH (RR = 0.84, 95% CI 0.43–1.65, $p = 0.61$) and oxygen therapy time (SMD = 0.03, 95% CI −0.33–0.39, $p = 0.88$) and had no significant difference than that in the NCPAP group.[50,65,72]

Recommendation notes: Based on the available evidence, comparing with NCPAP, HFNC after the INSURE strategy in preterm infants with gestational age ≥28 weeks could benefit the patients by reducing nasal trauma and air leak, without increasing the incidence of other complications. In addition, the 72 h reintubation rate showed no difference. The patients included in the RCTs were preterm infants at ≥28 weeks of gestation; therefore, it is recommended that HFNC can be used as an alternative to NCPAP after the INSURE strategy for preterm infants with gestational age ≥28 weeks. However, the sample size of the current studies was not large, and more high-quality, large multicenter RCTs are needed to support the safety and efficacy of using HFNC after the INSURE strategy. In addition, the application of HFNC in other minimally invasive PS delivery methods is a direction for future research.

Recommendation 5: Wean from NCPAP to HFNC is helpful for preterm infants with gestational age ≥ 28 weeks. (2C)

Evidence summary: The optimal protocol for weaning from NCPAP remains unclear. HFNC can be used for weaning from NCPAP.[92] The systematic review and meta-analysis (four RCTs, $n = 309$) developed by the guidelines development working group found that, when compared with direct weaning from NCPAP, weaning from NCPAP to HFNC in preterm infants can reduce the incidence of nasal trauma (RR = 0.47, 95% CI 0.26–0.84, $p = 0.01$) and shorten the NCPAP support time (SMD = −0.36, 95% CI −0.72 to 0.00, $p = 0.05$). Hospitalization (SMD = −0.90, 95% CI −2.58 to 0.77, $p = 0.29$), oxygen therapy

(SMD = −3.86, 95% CI −13.77 to 6.04, p = 0.44), and respiratory support time (SMD = 0.10, 95% CI −0.30 to 0.51, p = 0.62) presented no significant differences between the groups. The incidence of other complications including BPD (RR = 1.36, 95% CI 0.80−2.33, p = 0.25), NEC (RR = 0.66, 95% CI 0.19−2.27, p = 0.51), IVH (grade III-IV) (RR = 0.54, 95% CI 0.15−1.91, p = 0.34), and ROP (RR = 1.21, 95% CI 0.68−2.14, p = 0.51) also showed no significant difference.[93–96]

Recommendation notes: Based on the available evidence, weaning from NCPAP to HFNC can shorten the duration of NCPAP support and reduce the incidence of nasal trauma without increasing adverse outcomes. Thus, HFNC facilitates weaning from NCPAP. The four RCTs included preterm infants at ≥28 weeks of gestation, so it is recommended that HFNC can be used to wean from NCPAP in preterm infants ≥28 weeks' gestation. More high-quality clinical studies are needed to provide evidence that HFNC can help wean patients from NCPAP.

4.2 | Question 2: In what special cases can HFNC be used and what is the effect?

Recommendation 6: HFNC can be used for stabilization in the delivery room and then transfer to the NICU of preterm infants with gestational age ≥28 weeks. (2D)

Evidence summary: Three studies were included in this recommendation, including one observational study[97] and two retrospective studies.[98–99] The observational study (n = 28) found that 90% of preterm infants (gestational age ≤30 weeks) could be successfully stabilized with HFNC in the delivery room and transfer to the NICU using HFNC.[97] A retrospective study (n = 133) used HFNC to stabilize preterm infants (gestational age < 32 weeks) in the delivery room and found that 41% of the very preterm infants (n = 54) could be stabilized with HFNC. Compared with NCPAP, the gestational age of preterm infants under HFNC was lower (27+5 weeks (24 + 1 to 31 + 5) vs. 30 + 0 weeks (24 + 3 to 31 + 6), p < 0.001), while more preterm infants stabilized at air oxygen levels (21%) (43% vs. 22%, p = 0.03).[98] Another retrospective cohort study (n = 491) found that the percentage of intubation in the delivery room by using HFNC for stabilization was 19% for preterm infants <32 weeks, which was lower than the 31.5% reported by the Canadian Neonatal Network using standard procedure. Furthermore, the proportion of neonatal normothermia on admission was higher than that published on national data (83% vs. 70%). Furthermore, it found that 59% of very preterm infants (n = 292) were stable under HFNC, and HFNC stabilization rates were higher in this group (gestational age of 27−32 weeks) compared with extremely preterm infants (63% vs. 53%, p = 0.036).[99] Therefore, the risk of HFNC therapy for extremely preterm infants was supposed to be higher.

Recommendation notes: This recommendation is based on the advantages, cost-effectiveness, and family acceptance of HFNC in the delivery room compared to NCPAP. The advantages of HFNC include that it is easy to use and quick to apply and start in the delivery room. HFNC delivers a heated and humidified flow, which helps maintain body temperature. In addition, HFNC facilitates transfer and is comfortable for the patients, which was highly accepted by family members. Although limited, the available evidence suggests that HFNC can be used for delivery room stabilization and transfer of preterm infants. For extremely preterm infants, there may be risks in the use of HFNC in the delivery room after birth.[99] Therefore, it is recommended that preterm infants born at ≥28 weeks of gestation can use HFNC for delivery room stabilization and transfer.

Recommendation 7: HFNC can be used for neonatal transport of neonates with gestational age ≥ 28 weeks. (2D)

Evidence summary: Three observational studies were included in this recommendation.[100–102] An observational study (n = 102) found that in neonates who were transferred inter-hospital using HFNC (birth gestational age 28 (23-41) weeks, birth weight 970 (510–4320) g, transfer age 33(1-130) days), there was no difference in the flow of HFNC (L/min) (4.6 *vs.* 4.7, p = 0.31) and blood gas parameters including pH (7.350 vs. 7.353, p = 0.46) and PCO_2 (6.60 kPa vs. 6.66 kPa, p = 0.96) pre- and post-transfer, respectively.[100] A retrospective study (n = 1684) (median gestational age 37 (32-39) weeks, median birth weight 2680 (1470–3360) g) showed that neonates (n = 114) were all successfully transferred without the need for tracheal intubation or pneumothorax.[101] Another retrospective study (n = 195) showed that 97% of neonates were successfully transferred with HFNC; 3% needed to change respiratory support during transfer. Sixteen percent of neonates included in this study had a gestational age < 30 weeks, and 12% were very low birth weight infants.[102]

Recommendation notes: The use of HFNC for neonatal transport is increasing.[100,103] The limited available evidence suggests that HFNC is relatively safe for neonatal transport.[100,103] The condition and risk of the patient must be assessed before transfer. A retrospective study (n = 195) found that patients potentially requiring escalation of respiratory support had the following characteristics: higher pre-transfer FiO_2 (0.60 (0.36−1.00) vs. 0.36 (0.23−0.56)) and lower pre-transfer peripheral capillary oxygen saturation/fraction of inspired oxygen (SpO_2/FiO_2 < 200).[102] This recommendation does not apply to extremely preterm infants < 28 weeks gestation as they were critically ill with rapidly changing conditions. More high-quality evidence is needed for the inter-hospital transport of newborns using HFNC.

Recommendation 8: HFNC therapy during endotracheal intubation can improve the rate of successful neonatal intubation on the first attempt. (2B)

Evidence summary: This recommendation includes one multicenter RCT (n = 202),[104] which found that, compared to the standard-care group (no nasal high-flow therapy or supplemental oxygen), HFNC therapy during endotracheal intubation improved the likelihood of successful intubation on the first attempt (68.5% vs. 54.3%, 95% CI 4.32−7.3) and also led to a greater likelihood of successful intubation on the first attempt without physiological instability in neonates in the delivery room or NICU (50.0% vs. 31.5%, 95% CI 6.0−29.2). At the first intubation attempt, the median oxygen saturation in the HFNC group was higher than that in the standard-care group (93.5% vs. 88.5%, 95% CI 1.1−8.9).[104]

Recommendation notes: This recommendation is based on available evidence that HFNC therapy during endotracheal intubation can improve successful neonatal intubation on the first attempt. Endotracheal intubation is a common invasive procedure for neonatal

rescue. A large international multicenter study found that in 2617 intubations, the first-time success rate was <50%, and up to 48% of patients experienced severe oxygen desaturation during intubation.[105] An observational study found that only 17% of neonates were intubated within 20 s of resuscitation in the delivery room.[106] Intubation failure is associated with long-term intraventricular hemorrhage and neurodevelopmental deficits in preterm infants. A retrospective study of ELBW neonates ($n = 378$) intubated during delivery room resuscitation found that a successful first intubation may improve mortality or neurodevelopmental outcomes (28.6% vs. 52.8%, 95% CI 0.1–1.0).[107] Therefore, improving the success rate of intubation is important in the treatment of neonates. The assisted use of HFNC has been successfully applied to intubation in children and adults and can help maintain a normal physiological status. If used during anesthesia induction/recovery, the airway should be fully open and unobstructed to ensure ventilation. CO_2 retention may occur in patients receiving HFNC; therefore, routine use of transcutaneous CO_2 detection is recommended. More research and evidence are needed to verify its effectiveness in neonatal tracheal intubation and its impact on prognosis.

4.3 | Question 3: What are the contraindications of HFNC in clinical use?

Recommendation 9: Contraindications for the use of HFNC *mainly include (1) severe RDS, FiO_2 > 40%–60%; (2) severe apnea: frequent apnea (> 3 apnea within 1 h) after drug treatment or respiratory support; (3) congenital malformations, including choanal atresia, cleft lip and palate, esophagobronchial fistula, diaphragmatic hernia, and intestinal atresia.et.al; (4) maxillofacial trauma; (5) air leak syndrome including undrained pneumothorax, and pneumomediastinum.et.al; (6) upper airway injury or obstruction; (7) unstable condition, including hypotension and shock.et.al; (8) emergency situations that require endotracheal intubation, such as severe arrhythmia, and gastrointestinal bleeding.et.al.*[72,82,87,88,108] ***(GPS)***

Recommendation notes: No relevant original research evidence was found regarding this question. Currently available evidence comes from the expert consensus published in the European guidelines and an expert consensus published in China as well as the contraindications in the exclusion criteria involved in HFNC application schemes of different teams. In clinical practice, it is necessary to evaluate the patient condition, weigh the pros and cons, and reduce injuries in neonates. The guidelines development working group used the Delphi consultation method to collect 31 expert feedbacks, with an agreement rate of 96.9% for this recommendation. Based on the consensus and opinions of experts, as well as the current situation and clinical experience, this recommendation was finally reached.

4.4 | Question 4: How to perform initial parameter setting and adjustment when using HFNC?

Recommendation 10: The flow of HFNC can be adjusted in the range of 2–8 L/min, and the inspired oxygen concentration is the lowest oxygen concentration needed to reach the target oxygen saturation. (GPS)

Evidence summary: This recommendation includes 12 articles, including 1 guideline,[87] 2 expert consensus,[88,109] and 9 RCTs.[54,61,62,64,66,72,79,82,89,110] Different research centers often set the initial parameters in the following ways: initial flow was set according to neonatal weight, disease severity was assessed, or initial flow setting was adjusted according to the clinical effect.[54,61,62,64,66,72,79,82,89,110] The "Oxford HFNC Guidelines" suggested that in neonates <1500 g, the initiation of flow was set to 4–6 L/min; in neonates 1500–3000 g, it was 5–7 L/min; and in neonates > 3000 g, it was 6–8 L/min.[87] According to an experts consensus (2017), there was general agreement for an initial flow of 4–6 L/min.[109] The consensus of experts in China recommends that the initial oxygen concentration could be set at 30%–40% and the initial flow could be set at 3–6 L/min for neonates weighing 1000–1999 g, 4–7 L/min for neonates weighing 2000–2999 g, and 5–8 L/min for neonates weighing >3000 g,[88] which was adjusted according to the clinical response. Generally, flow should be increased when the symptoms of respiratory distress are aggravated or oxygen demand increases; otherwise, flow is decreased. Initial flow was increased by 1 L/min in the following situations: FiO_2 increased by 10% compared with baseline, partial pressure of CO2 (PCO_2) increased by 10 mmHg compared with baseline, and dyspnea worsened. When the parameters and respiratory status are stable for > 12–24 h, they can be lowered.[109] Initial flow was reduced by 0.5–1 L/min in the following situations: FiO_2 < 30%, SaO_2 within the target range, PCO_2 maintained within the allowable range, and no obvious respiratory distress. The FiO_2 was gradually set to the lowest oxygen concentration to reach the target SaO_2.[62,64,66,82]

Recommendation notes: The currently available evidence comes from the published consensus and the parameter setting and adjustment methods involved in different research programs on HFNC application. The guidelines development working group used the Delphi consultation method to collect feedback from 30 experts, with an agreement rate of 93.7% for this recommendation. This recommendation was finally reached after integrating expert consensus, clinical experience, and the feasibility of clinical implementation.

Recommendation 11: The target of the HFNC heated and humidified gas is 37°C and 100% relative humidity. (GPS)

Evidence summary: Two guidelines were included in this recommendation.[85,87] AAP suggests that when HFNC is used in preterm infants, the inhaled gas should be warmed and humidified to normal airway gas conditions (37°C and 100% RH) in advance.[85] The "Oxford HFNC Guidelines" recommend an optimum temperature setting of 37°C; however, when the gas flow is < 4 L/min and there is condensed water in the respiratory circuit, the temperature can be adjusted down to 34–35°C.[87]

Recommendation notes: No relevant original research evidence was found; therefore, the available evidence came from published guidelines. This guidelines development working group used the Delphi consultation method to collect expert feedbacks, with an agreement rate of 90.6% for this recommendation. This recommendation was finally reached after integrating expert consensus

and clinical experience. Additionally, the temperature and RH of the supplied HFNC flow depend on ambient temperature. Compared with the respiratory circuit placed in the incubator at 37°C, the gas temperature (36.9 ± 0.2°C vs. 26.1 ± 0.6°C, $p < 0.01$) and absolute humidity (35.5 ± 0.7 mg/L vs. 16.5 ± 1.0 mg/L, $p < 0.01$) in the respiratory circuit will drop when the incubator is turned off for heating.[111] Therefore, when the ambient temperature drops, an increase in condensed water in the circuit may affect ventilation efficiency.

4.5 | Question 5: What is the weaning protocol of HFNC?

Recommendation 12: HFNC can be weaned when the clinical state is stable, with an inspired oxygen concentration < 30%, a flow < 2 L/min, and maintained for more than 12–24 h. (GPS)

Evidence summary: This recommendation included one consensus[88] and three RCTs.[62,79,110] The adopted HFNC weaning standards were as follows: the clinical state of the patient was stable, FiO_2 < 30%, flow < 2 L/min, and maintained for more than 12–24 h.[62,79,110] The 2017 Chinese HFNC consensus suggested that when FiO_2 < 30%, neonates < 1500 g have a flow < 1 L/min, neonates > 1500 g have a flow < 2 L/min without respiratory distress or dyspnea, SpO_2 > 90%, and $PaCO_2$ is maintained at an acceptable level, weaning may be considered.[88]

Recommendation notes: No relevant original research evidence was found, and the weaning criteria varied across studies. The guidelines development working group used the Delphi consultation method based on the weaning schemes involved in different HFNC studies, expert consensus, and clinical experience to collect expert feedback ($n = 29$) with an agreement rate of 90.6% for this recommendation. This recommendation was finally reached after a comprehensive expert consensus and the feasibility of clinical implementation. It is recommended that patients with stable clinical status, FiO_2 < 30%, and flow rate < 2 L/min, that is maintained for > 12–24 h, can be weaned of HFNC. According to the existing literature and clinical experience, HFNC weaning has the following strategies: stop directly under the original parameters, gradually reduce HFNC to the predetermined parameters and then stop, gradually reduce the running time under the original parameters every day until it stops completely, sequential low-flow oxygen inhalation after weaning, and a combination of these strategies according to each patient's condition.[24] However, standardized weaning may be more beneficial than empirical weaning from HFNC. An observational study (n = 104) found that, compared with the empiric weaning group, the HFNC weaning failure rate in the protocol weaning group was lower (7.8% vs. 28.3%, $p = 0.007$), and the time to reach full enteral feeding was shorter (7 vs. 8 days, $p = 0.03$).[112] When weaning from HFNC, it should be considered whether it is necessary to use low-flow oxygen therapy, such as nasal catheter oxygen inhalation, depending on the clinical situation of the patient. After weaning, attention should be paid to changes in vital signs and respiratory status; blood gases should be re-checked or monitored for noninvasive transcutaneous carbon dioxide pressure (T_CPCO_2).

4.6 | Question 6: What conditions suggest that HFNC treatment is ineffective? How to deal with it?

Recommendation 13: HFNC treatment is ineffective when any of the following criteria are reached.

While maximum flow reaches 8 L/min and FiO_2 > 40%–60%, and the target SaO_2 is unable to be maintained; frequent apnea occurs after drug treatment or respiratory support; arterial blood gas shows severe respiratory acidosis or metabolic acidosis; increased work for breathing; and emergency intubation is required.

When HFNC is ineffective, other noninvasive ventilation such as NCPAP or mechanical ventilation can be used as rescue treatment. (GPS)

Evidence summary: This recommendation includes 11 RCTs.[54,61,62,64,66,72,80,83,96,110] Combining the criteria for judging the ineffectiveness of HFNC treatment involved in the studies of different HFNC application programs, it is indicated that HFNC treatment is ineffective when any of the following criteria are reached: ① When the maximum flow rate is 8 L/min, FiO_2 > 40%–60%, and still unable to maintain the target SaO_2; ② frequent apnea (> 3 times or 1 apnea requiring balloon positive pressure ventilation within 1 h) still occurs after drug treatment or respiratory support; ③ arterial blood gas indicates severe respiratory acidosis or metabolic acidosis (PH < 7.25 or PCO_2 > 60 mmHg); ④ increased breathing work, including faster breathing, work of auxiliary respiratory muscles, moaning, and aggravation of three concave signs; ⑤ intubation is required in emergencies.[54,61,62,66,72] During HFNC treatment, it is necessary to pay close attention to changes in the patient's condition. A multicenter RCT ($n = 372$) found that rescue treatment with NCPAP or NIPPV in preterm infants <34 weeks postextubation failure with HFNC did not increase reintubation rates (5.7% vs. 8.7%, 95% CI −8.3 to 2.4, $p = 0.29$).[110] Many studies have shown that when HFNC treatment fails, NCPAP or other noninvasive assisted ventilation and mechanical ventilation can be used as rescue treatment to avoid delaying rescue time.[64,80,83,96,110]

Recommendation notes: No relevant original research evidence was found, and the currently available evidence comes from the failure criteria adopted in the HFNC application scheme in different studies and from expert consensus. The guidelines development working group used the Delphi consultation method to collect feedback from 31 experts, with an agreement rate of 96.9% for this recommendation, and finally reached this recommendation.

4.7 | Clinical Question 7: How to reduce related complications?

Recommendation 14: Nasal prongs <50% of the nostril diameter should be used to reduce the risk of barotrauma. (GPS)

Evidence summary: This recommendation includes two references: one guideline[87] and one observational study.[113] Nasal prongs appropriately proportioned to the nostrils of neonates should be selected for safe and effective use of HFNC. A large ratio between the outer diameter of the nasal prongs and inner diameter of the nostril may result in excessive pressure, which is associated with an increased risk of barotrauma. Airway pressure gradually increases as the ratio between the outer diameter of the nasal prongs of HFNC and the inner diameter of the nostril of infants increases and could be as high as 24 cmH_2O when the ratio is 1.0.[113] The Oxford HFNC Guidelines recommend that the diameter of the nasal prongs should be <50% of the internal diameter of the nostril to allow adequate gas leakage in case of high pressure, which can diminish the risk of barotrauma.[87]

Recommendation notes: This recommendation is based on the available literature and the results obtained from the in vitro study of HFNC. This recommendation had a low level of evidence; however, it is recommended to use nasal plugs < 50% of the nostril diameter to decrease the risk of barotrauma, considering the importance of safe device use during clinical HFNC implementation. The guidelines development working group collected feedback from 32 experts using the Delphi method, and the agreement rate was 100% for this recommendation, finally contributing to the formulation of this recommendation. Additionally, a pressure relief valve is required to avoid the delivery of excessive pressure with HFNC.[33,114] Therefore, if available, medical units can also use a pressure relief valve in the cannula to reduce the risk of barotrauma.

Recommendation 15: The HFNC circuit should be replaced when they are damaged or contaminated to prevent nosocomial infections. (GPS)

Evidence summary: This recommendation includes two references: one guideline[115] and one prospective study.[116] The warmth and humidity of the flow improves mucociliary function, but warm and humid conditions also promote bacterial growth. The included prospective study explored the occurrence of contamination in the pipeline after discontinuation of HFNC by sampling from the interface and the chamber ends of the circuit, revealing five positive cultures among the 31 collected samples, indicating circuit contamination.[116] The Guidelines for the Prevention and Treatment of Ventilator-Associated Pneumonia in China stated that ventilation circuits do not need to be replaced regularly, but should be promptly replaced if damaged or contaminated, and that disposable components should be discarded after its use in accordance with relevant regulations and in an environmentally safe manner.[115]

Recommendation notes: This recommendation is based on the existing literature. Considering the cost-benefit and clinical influence of replacing the HFNC circuit, the limited available evidence recommends prompt replacement of the HFNC circuit when damaged or contaminated. If a disposable HFNC circuit was used, they should be disposed after use according to relevant regulations, and repeated use should be prohibited. The guidelines development working group collected 29 expert feedbacks using the Delphi method and the agreement rate was 90.6% for this recommendation. Additionally, circuit disconnection should be avoided during ventilation to reduce contamination.

4.8 | Clinical Question 8: What are the effects and benefits of HFNC compared to other noninvasive ventilation modes?

Recommendation 16: HFNC has similar effectiveness to NCPAP when used for the primary noninvasive respiratory support of neonates. (2B)

HFNC is less effective than NIPPV when used for tehe primary noninvasive respiratory support of preterm infants. (1B)

HFNC is less effective than NCPAP when used for postextubation respiratory support of neonates. (1B)

In addition to NCPAP, other new noninvasive respiratory support modes including bilevel positive airway pressure (BiPAP), NIPPV, and nasal high-frequency oscillation ventilation (NHFOV) have been increasingly used in neonates.

Evidence summary: A systematic review and meta-analysis based on 22 RCTs (n = 3807) was developed by the guidelines development working group. This analysis showed that there was no difference in the treatment failure rates (RR = 1.24, 95% CI 0.94–1.62, p = 0.12) between HFNC and NCPAP when used for the primary noninvasive respiratory support of neonates.[48,49,51,53–70,72] Additionally, a systematic review and meta-analysis based on 22 RCTs (n = 3832) developed by the guidelines development working group also showed no significant difference in the mechanical ventilation rate between the HFNC and NCPAP groups (RR = 1.02, 95% CI 0.87–1.20, p = 0.77).[48-51,53-56,58-70,72] Moreover, subgroup analyses (2 RCTs, n = 38) of extremely preterm infants (gestational age < 28 weeks) showed no significant difference in intubation rates between the HFNC and NCPAP groups (RR = 0.43, 95% CI 0.15–1.24, p = 0.12).[54,64]

A network meta-analysis (35 RCTs, n = 4078) was conducted to compare different noninvasive modes for the primary treatment of preterm infants with NRDS, which demonstrated that HFNC was associated with a higher risk of treatment failure (1 RCT, n = 89, gestational age 28–32 weeks; RR = 0.43, 95% CI 0.30–0.63) and a higher rate of mechanical ventilation (2 RCTs, n = 165, gestational age < 35 weeks; RR = 0.66, 95% CI 0.43–0.97) than NIPPV.[117]

A systematic review and meta-analysis developed by the guidelines development working group based on six RCTs (n = 952) showed that HFNC was associated with a higher treatment failure rate (RR = 1.47, 95% CI 1.16–1.86, p = 0.002) compared to NCPAP for postextubation respiratory support of neonates.[50,62,79–81,83] However, the 72 h reintubation rate presented no significant difference between the HFNC and NCPAP groups (RR = 1.24, 95% CI 0.78–1.97, p = 0.37) based on six RCTs (n = 476), which may be related to the use of NCPAP and other noninvasive ventilation as rescue treatment after HFNC fail.[50,65,72,80,81,84] The results of a multicenter RCT (n = 338) comparing HFNC and NHFOV showed that the failure rate of extubation was significantly lower in the NHFOV group than in the HFNC group (10.8% vs. 23.3%, p < 0.05) for preterm infants (gestational age < 32 weeks), but this was not statistically significant between both groups for preterm infants at gestational age 32–36 weeks (8.2% vs. 11.8%, p > 0.05).[118]

Recommendation notes: This recommendation was obtained based on the available evidence. HFNC has similar effects to NCPAP for the initial noninvasive respiratory support of neonates but were lower than those of NIPPV. HFNC is less effective than NCPAP for postextubation respiratory support in neonates, which may be related to the relatively large amount of research data on extremely preterm infants included in the meta-analysis. Therefore, the available evidence does not recommend the use of HFNC after extubation in extremely preterm infants. Few studies have been conducted to compare the effects of HFNC and NHFOV, which merits more high-quality clinical studies to provide evidence-based results.

Recommendation 17: HFNC reduces nasal trauma compared with NCPAP. (1A)

Evidence summary: Noninvasive respiratory support often leads to nasal trauma owing to the use of nasal plugs. The guidelines development working group conducted a systematic review and meta-analysis (26 RCTs, $n = 4189$) on primary noninvasive respiratory support after birth and postextubation respiratory support, and observed that the incidence of nasal trauma was lower in the HFNC group than in the NCPAP group (RR = 0.45, 95% CI 0.39–0.53, $p < 0.00001$).[46,48–50,52–56,58–60,62,65,66,68–72,78–82,84]

Recommendation notes: This recommendation is based on existing evidence demonstrating that HFNC is associated with less nasal skin and mucosal injury than NCPAP. Therefore, if neonates are at a high risk of nasal trauma or have already developed nasal trauma when other noninvasive respiratory support was needed, the clinical status and disease severity of neonates could be assessed and HFNC treatment considered because of the low risk of nasal trauma or the degree of injury.

Recommendation 18: HFNC reduces air leakage compared with NCPAP in neonates. (1A)

Recommendation 19: The incidence of air leakage in HFNC is similar to that in NIPPV in preterm infants. (2C)

Evidence summary: Air leakage may occur during noninvasive respiratory support.[119–121] This guidelines development working group performed a systematic evaluation and meta-analysis (29 RCTs, $n = 4850$) of primary noninvasive respiratory support after birth and postextubation respiratory support in neonates, which revealed that the incidence of air leakage was lower in the HFNC group (RR = 0.56, 95% CI 0.41–0.76, $p = 0.001$) than in the NCPAP group.[46,47,49,50,52,54–56,58–72,77,79–83] A network meta-analysis that compared different noninvasive modes for the primary treatment of preterm infants with NRDS (35 RCTs, $n = 4078$) showed no significant difference in the incidence of air leakage (RR = 0.85, 95% CI 0.39–1.94) between the HFNC and NIPPV groups (two RCTs, $n = 165$, gestational age < 35 weeks).[117]

Recommendation notes: This recommendation was developed based on the available evidence indicating that HFNC reduces risk of air leakage in neonates than NCPAP, and that the incidence of air leakage caused by HFNC and NIPPV is similar in preterm infants. Therefore, HFNC can be used as an alternative to other noninvasive respiratory support methods for neonates at a high risk of air leakage when clinically stable.

Recommendation 20: HFNC is easier to operate and more convenient for nurses compared to NCPAP. (GPS)

Recommendation 21: HFNC is more comfortable compared with NCPAP. (1D)

Evidence summary: HFNC is easier to operate than NCPAP in the care of neonates by nurses.[122] This recommendation includes four articles, including one randomized study[123] and three observational studies.[124–126] The observational study has shown that HFNC-treated preterm infants had lower preterm infant pain profile scores (4 (2–6) vs. 10 (7–12), $p < 0.01$) and fewer cried times (11 (47.8%) vs. 30 (81.1%), $p < 0.001$) than NCPAP-treated infants.[124] The included randomized study evaluated neonatal comfort with the Echelle Douleur Icon Nouveau-Né (EDIN) scale, a neonatal pain and discomfort scale, which revealed that the cumulative EDIN score was non-significantly lower in the HFNC group than in the NCPAP group (10.7 vs. 11.1, $p = 0.35$). However, families preferred HFNC to NCPAP ($p < 0.05$), which is probably due to several factors: neonates are more comfortable; families can easily access and interact with neonates; and HFNC is easy to operate, thus increasing the feasibility of the family participating in caring activities.[123] Another observational study ($n = 42$) evaluated the comfort of neonates treated with HFNC and NCPAP and their satisfaction with different scales and illustrated that EDIN scores (7 vs. 8.5, $p > 0.05$) were lower, but the visual analog scale scores for familiar satisfaction, ease of communication with neonates, and the need of neonates for care by a nurse were higher in the HFNC group than in the NCPAP group ($p < 0.05$).[126] A questionnaire survey of the nurses staff for the evaluation of HFNC and NCPAP as postextubation respiratory support for preterm infants with gestational age < 32 weeks reported that HFNC was easier to operate, more comfortable for neonates, less likely to cause nasal injury, and more acceptable to families than NCPAP.[125]

Recommendation notes: This recommendation was based on the available literature. Considering the feasibility and safety of the clinical implementation of HFNC, as well as the comfort of neonates and the acceptance of their families, the limited available evidence illustrates that HFNC is easier to operate by nurses caring for neonates, comfortable for neonates, and is more satisfying for their families. The guidelines development working group collected 31 expert feedbacks using the Delphi method and the agreement rate was 96.9% for this recommendation. Hence, when neonates are irritable and not easily soothed under other noninvasive ventilation methods, HFNC can be used as an alternative after the condition of the neonates is assessed, to increase comfort and reduce crying. Additionally, HFNC can be used for kangaroo or home-based care wards to allow for greater family involvement.

4.9 | Clinical Question 9: How is nebulization therapy given during HFNC?

Recommendation 22: A vibrating mesh nebulizer (VMN) is recommended for increased aerosol deposition compared to other nebulizers. (2D)

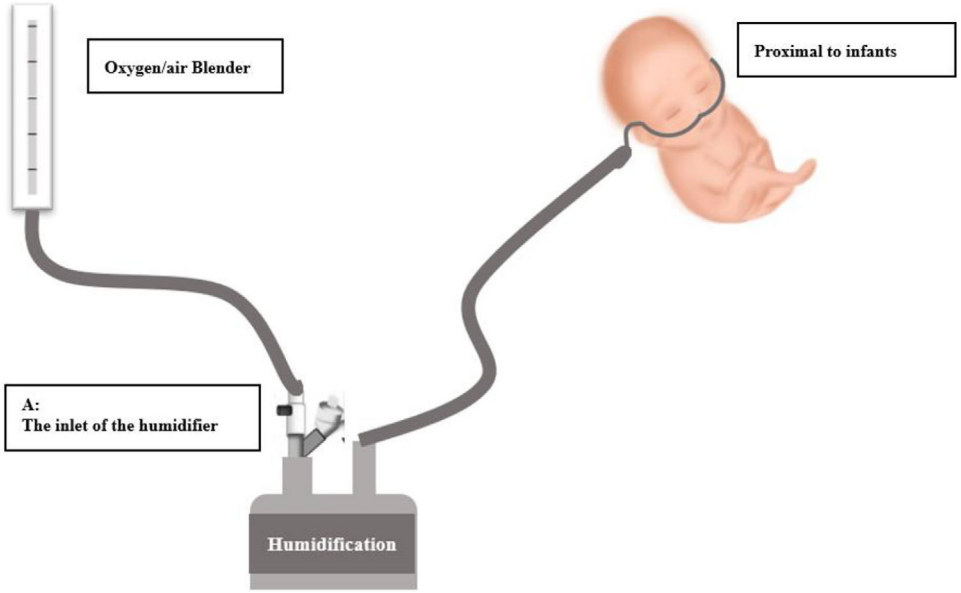

FIGURE 2 The nebulizer is placed proximal to the humidifier (inlet).

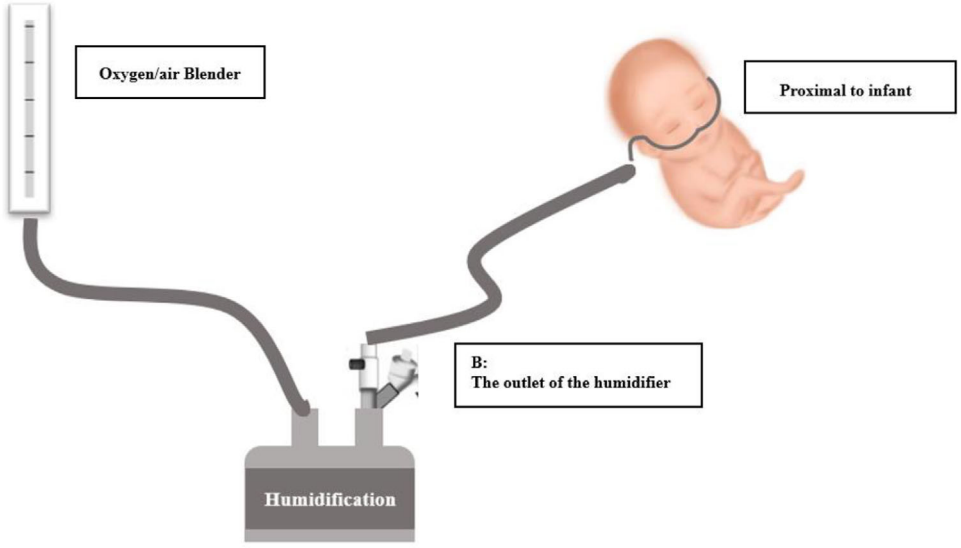

FIGURE 3 The nebulizer is placed proximal to the humidifier (outlet).

Recommendation 23: It is recommended to place the nebulizer proximal to the inlet or outlet of the humidifier for greater aerosol deposition. (2D)

Recommendation 24: During nebulization, it is recommended to set the HFNC flow to 1.0–2.6 L/min for higher aerosol deposition. (GPS)

Evidence summary: In recent years, aerosol delivery via HFNC has been increasingly used, which combines the advantages of HFNC and aerosol therapy. A survey of children's hospitals in the United States reported that 75% of respondents received aerosol therapy during HFNC.[127] The type, placement, gas flow rate, carrier gas of nebulizers, and size of nasal cannulas affect the actual drug delivery efficiency.[128,129] Currently, several commonly used nebulizers exist, including jet nebulizers (JNs), ultrasonic nebulizers (USNs), and Vibrating Mesh Nebulizers (VMNs).

Recommendations regarding the type of nebulizer include one RCT[130] and one in vitro observational study,[131] which demonstrated that VMN produced 2–3 times more aerosol deposition than JNs when combined with HFNC.[130,131]

The recommendations for the placement of nebulizers include two in vitro observational studies,[132,133] which showed that aerosol deposition was higher when the VMN was placed at the proximal end of the humidifier (the inlet or outlet of the humidifier) (Figures 2 and 3) than when it was placed proximal to the infants under conventional high-flow setting parameters.[132,133]

TABLE 3 Peak inspiratory flow in neonates of different weights and flow settings for nebulized drug delivery via HFNC.

Weight range (g)	Peak inspiratory flow (L/min)	Flow for nebulized drug delivery via HFNC (L/min)
500–1000	2.1	1.0
2001–2500	3.5	1.7
2501–5000	5.2	2.6

To recommend HFNC flow during nebulization, five observational studies were included.[129,131,134–136] During treatment, a higher flow can dilute the aerosol in the circuit and elevate the turbulence, resulting in a loss of the aerosol, thereby diminishing the dose delivered to the airways and alveoli of infants.[129] Several in vitro studies demonstrated that aerosol deposition is inversely proportional to flow.[131,134] Therefore, higher aerosol deposition can be achieved by reducing the flow of HFNC during nebulization. The proportion of HFNC flow to the peak inspiratory flow of infants may be more important than the flow of HFNC alone, with higher aerosol deposition observed when the HFNC flow is set below 50% of the peak inspiratory flow of infants.[135,136] Furthermore, the peak inspiratory flow of neonates was correlated with body weight (Table 3).[36] This guideline recommends that the HFNC flow during nebulization can be set with reference to Table 3 when the condition of the neonates is stable.

Recommendation notes: This recommendation is formulated based on the available evidence as well as the current status and clinical use in China and internationally. JN is usually driven by an additional gas source; therefore, the actual volume of air inhaled by neonates is the flow of HFNC plus the flow of the driving gas source, which leads to changes in the oxygen concentration, total gas flow, and gas pressure in the airway, thus posing potential risks. Conversely, the USN and VMN are powered by electricity without the influence of additional gases. Nevertheless, USN can heat the liquid during nebulization; therefore, it is not applicable for nebulizing protein- or peptide-containing drugs. The drug solution for the VMN was released as aerosol particles through tiny meshes of a fixed diameter. Compared to USN and JN, VMN releases smaller and more uniform drug particles; therefore, it is recommended as the preferred choice for aerosol treatment. However, owing to the high cost of VMN consumables, an appropriate nebulizer can be selected clinically to obtain the expected results based on actual needs, nebulizer characteristics, and cost-benefit. It is recommended to place the nebulizer proximal to the inlet or outlet of the humidifier to achieve a higher inhalation dose. When the condition is stable, the HFNC flow can be set depending on the body weight of the neonates to enhance drug deposition.

4.10 | Cost-benefit analysis

HFNC reduces hospitalization costs compared to NCPAP. (D)

Summary of evidence: This recommendation includes one systematic review,[25] one RCT,[84] and one retrospective cohort study.[137] The systematic review integrated health technology assessment, where a cost analysis was conducted by comparing the cost of consumables, the human cost of implementing the operation, and the resources required for adverse event management, and demonstrated 5% cost savings with the use of HFNC over NCPAP after extubation.[25] RCT in China ($n = 94$) was performed to compare the cost difference between the use of HFNC and NCPAP in preterm infants after extubation; HFNC markedly decreased hospitalization costs ($p < 0.05$).[84] A retrospective cohort analysis ($n = 79$) in the United Kingdom indicated that healthcare costs decreased by 21%–23% for combination treatment with NCPAP and sequential HFNC compared to direct withdrawal from NCPAP.[137]

Rationale and explanation: The cost of respiratory support therapy accounts for a large proportion of the cost of hospitalization for NRDS; therefore, the cost-benefit of respiratory support therapy is of particular concern. Existing evidence indicates that HFNC can decrease medical costs compared with NCPAP alone, whether used in the primary treatment, after extubation, or as the sequential treatment of NCPAP. Additionally, the potential risks associated with nasal injury, as well as the consequence analysis, were not included in the abovementioned economic analysis; the use of HFNC can substantially reduce the incidence of nasal injury among adverse reactions compared to the remaining noninvasive ventilation modes. Consequently, the overall benefits of HFNC may be underestimated.

5 | SUMMARY

As HFNC is widely used in NICUs in China, its standardized use is essential for promoting neonates' recovery and ensuring medical safety. Among the noninvasive ventilation techniques, HFNC has unique advantages including being easier to operate and more convenient for nurses, greater comfort for neonates, and lower incidence of nasal trauma and air leakage, although it may have lower respiratory support effects. In clinical practice, the coordination between neonates and ventilators should be considered during the treatment. Keeping the neonates comfortable and quiet is more important to guarantee effectiveness than receiving superior respiratory support modes. Therefore, individualized noninvasive support protocols should be used. The clinical conditions of the neonates need to be closely monitored during respiratory support. Other noninvasive respiratory supports or mechanic ventilation should be considered as rescue therapy if necessary. These guidelines aim to help medical practitioners understand the characteristics of different noninvasive ventilation modes and implement a stepwise individualized, noninvasive support program in clinical practice. Thus, cycling through various noninvasive ventilation modes during respiratory support, satisfying the oxygenation and ventilation needs of neonates with minimal and optimal respiratory support, and improving the comfort of neonates while reducing medical costs. Recently, HFNC has been increasingly used not only in NICUs but also in delivery rooms and in- and out-of-hospital transfers. Likewise, HFNC is gradually being used by medical centers for kangaroo mother care and home-based oxygen therapy. Hence,

TABLE 4 Recommendations of the guidelines for high-flow nasal cannula oxygen therapy in neonates (2022).

Clinical question	Recommendations	Level of evidence and recommendation[a]
What are the clinical indications for HFNC?	HFNC can be used as an alternative to NCPAP for primary respiratory support for neonates with gestational age ≥ 28 weeks.	2B
	HFNC can be used as an alternative to NCPAP for postextubation of neonates with gestational age ≥28 weeks.	2B
	HFNC can be used as an alternative to NCPAP for the treatment of apnea in preterm infants with gestational age ≥ 28 weeks.	2D
	HFNC can be used as an alternative to NCPAP for noninvasive ventilation after INSURE strategy of preterm infants with gestational age ≥ 28 weeks.	2C
	Wean from NCPAP to HFNC is helpful for preterm infants with gestational age ≥ 28 weeks.	2C
In what special cases can HFNC be used and what is the effect?	HFNC can be used for stabilization in the delivery room and then transfer to NICU for preterm infants with gestational age ≥ 28 weeks.	2D
	HFNC can be used for neonatal transport of neonates with gestational age ≥ 28 weeks.	2D
	HFNC therapy during endotracheal intubation can improve the rate of successful neonatal intubation on the first attempt.	2B
What are the contraindications to the clinical use of HFNC?	Contraindications to the use of HFNC mainly include (1) severe RDS, FiO_2 > 40%–60%; (2) severe apnea: frequent apnea (> 3 apnea within 1 h) after drug treatment or respiratory support; (3) congenital malformations, including choanal atresia, cleft lip and palate, esophagobronchial fistula, diaphragmatic hernia, and intestinal atresia.et.al; (4) maxillofacial trauma; (5) air leak syndrome including undrained pneumothorax, and pneumomediastinum.et.al; (6) upper airway injury or obstruction; (7) unstable condition, including hypotension and shock.et.al; (8) emergency situations that require endotracheal intubation, such as severe arrhythmia and gastrointestinal bleeding.et.al.	GPS
How to perform initial parameter setting and adjustment when using HFNC?	The flow of HFNC can be adjusted in the range of 2–8 L/min, and the inspired oxygen concentration is the lowest oxygen concentration to reach the target oxygen saturation.	GPS
	The target of the HFNC heated and humidified gas is 37°C and 100% relative humidity.	GPS
What is the weaning protocol of HFNC?	HFNC can be weaned when the clinical state is stable, with an inspired oxygen concentration < 30%, a flow < 2 L/min, and maintained for more than 12–24 h.	GPS
What conditions suggest that HFNC treatment is ineffective? How to deal with it?	HFNC treatment is ineffective when any of the following criteria are reached: While maximum flow rate reaches 8 L/min and FiO_2 > 40%–60%, the target SaO_2 is unable to be maintained, frequent apnea occurs after drug treatment or respiratory support, arterial blood gas shows severe respiratory acidosis or metabolic acidosis, increased work for breathing, and emergency intubation is required. When HFNC is ineffective, other noninvasive ventilation such as NCPAP or mechanical ventilation can be used as rescue treatment.	GPS
How to reduce related complications?	Nasal prongs < 50% of the nostril diameter should be used to reduce the risk of barotrauma.	GPS
	The HFNC circuit should be replaced when they are damaged or contaminated to prevent nosocomial infections.	GPS
What are the effects and benefits of HFNC compared to other noninvasive ventilation modes?	HFNC has similar effectiveness to NCPAP when used for the primary noninvasive respiratory support of neonates.	2B
	HFNC reduces nasal trauma compared with NCPAP.	1A
	HFNC reduces air leakage compared with NCPAP in neonates.	1A
	The incidence of air leakage in HFNC is similar to that in NIPPV in preterm infants.	2C
	HFNC is easier to operate and more convenient for nurses compared to NCPAP.	GPS
	HFNC is more comfortable compared with NCPAP.	1D
How is nebulization therapy given during HFNC?	A vibrating mesh nebulizer (VMN) is recommended for increased aerosol deposition compared to other nebulizers.	2D
	It is recommended to place the nebulizer proximal to the inlet or outlet of the humidifier for greater aerosol deposition.	2D
	During nebulization, it is recommended to set the HFNC flow to 1.0–2.6 L/min for higher aerosol deposition.	GPS

[a]A, B, C, and D mean that the quality level of evidence is high, moderate, low, very low; GPS means Good Practice Statement; 1 and 2 mean strong and weak recommendation, respectively.

issues related to HFNC should be addressed in future research. Currently, the safety and efficacy of HFNC in extremely preterm infants (gestational age < 28 weeks) require further investigation.

The recommendations of these guidelines are summarized in Table 4. These guidelines have 24 recommendations for nine clinical questions, including two recommendations at level A (8.3%), four recommendations at level B (16.7%), three recommendations at level C (12.5%), six recommendations at level D (25%), and nine recommendations at level GPS (37.5%). Although there were many RCTs included in the guidelines, these trials focused on certain study fields, which downgraded the evidence. Most of the recommendations were related to specific clinical practice, causing a high percentage of low-grade evidence. These guidelines were developed based on current evidence and extensive consultation with neonatologists, nurse specialists, respiratory therapists, anesthesiologists, evidence-based medical experts, and other peer experts; it weighs the pros and cons and optimizes the experience of its use for clinical reference.

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ILLUSTRATION

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CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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