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REVIEW

Noninvasive positive pressure ventilation in acute asthmatic attack

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ABSTRACT: Asthma is characterised by reversible airway obstruction. In most patients, control of disease activity is easily achieved. However, in a small minority, asthma may be fatal. Between the two extremes lie patients with severe asthmatic attacks, refractory to standard treatment. These patients are at an increased risk of recurrent severe attacks, with respiratory failure, and mechanical ventilation.

Invasive mechanical ventilation of the asthmatic patient is associated with a higher risk of complications and, therefore, is a measure of last resort.

Noninvasive positive pressure ventilation (NPPV) is another treatment modality that may be beneficial in patients with severe asthmatic attack who are at an increased risk of developing respiratory failure. These patients have the potential to benefit from early respiratory support in the form of NPPV. However, reports of NPPV in asthmatic patients are scarce, and its usage in asthmatic attacks is, therefore, still controversial. Only a few reports of NPPV in asthma have been published over the last decade. These studies mostly involve small numbers of patients and those who have problematic methodology.

In this article we review the available evidence for NPPV in asthma and try to formulate our recommendations for NPPV application in asthma based on the available evidence and reports.

KEYWORDS: Asthma, asthma clinical care, noninvasive mechanical ventilation

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Asthma is characterised by reversible airway obstruction caused by a triad of bronchial smooth muscle contraction, airway inflammation and increased secretions. In most patients, control of disease activity is easily achieved [1, 2]. However, in a small minority, asthma may be fatal [3]. Between the two extremes are patients with severe asthmatic attacks, who are refractory to standard treatment, steroid dependent and frequently admitted to emergency room departments and, consequently, a substantial burden on healthcare systems [4, 5]. These factors are known predictors of recurrent severe attacks, mandating extra caution by the physician, with need of closer monitoring and at times intensive care unit (ICU) admission, and, as a last resort, mechanical ventilation.

Invasive mechanical ventilation of the asthmatic patient is a challenge to the intensivist, and often necessitates permissive hypercapnia [6, 7], deep sedation and, at times, neuromuscular blockade.

Despite these protective approaches, mechanically ventilated asthmatic patients are at higher risk for complications such as barotrauma, nosocomial infections, muscle weakness, increased length of hospital stay and increased mortality [8–10]. These patients are often difficult to ventilate, have low compliance with high inspiratory pressures and have frequent patient–ventilator asynchrony [11]. Invasive mechanical ventilation is therefore a measure of last resort. Nevertheless, it should be applied promptly when needed. Thus, patients who are refractory to standard treatment and who are at risk for respiratory failure should be identified sooner rather than later. These patients have the potential to benefit from early respiratory support in the form of noninvasive positive pressure ventilation (NPPV).

In recent years NPPV has gained wide acceptance and is now used more frequently. It has been shown to be beneficial for a variety of clinical conditions. Previous studies have demonstrated the efficacy of NPPV in acute exacerbation of chronic obstructive pulmonary disease (COPD) [12, 13], acute cardiogenic pulmonary oedema [14, 15], hypoxaemic respiratory failure [16], immunocompromised

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patients [17, 18], as an adjunct to weaning patients [19, 20] and in weaning patients with COPD [21]. However, reports of NPPV in asthmatic patients are scarce, and its usage in asthmatic attacks is, therefore, still controversial.

EFFECTS OF AND RATIONALE FOR APPLICATION OF POSITIVE PRESSURE IN ASTHMA

As an asthmatic attack progresses there is an increase in obstruction and tachypnea resulting in a relatively short expiratory time with expiratory airflow limitation which culminates in dynamic increase in end-expiratory lung volume. The end result is positive end-expirartory pressure (PEEP), termed intrinsic or auto-PEEP; a phenomenon that is also referred to as dynamic hyperinflation. In the presence of auto-PEEP intrathoracic pressure is positive at end-expiration [22, 23]. As a result, in order to achieve airflow during inspiration, the patient must generate additional negative intrathoracic pressure to overcome their auto-PEEP [24–26]. This places a substantial burden on the inspiratory muscles, reducing their mechanical efficiency and leading to increased work of breathing, which further contributes to muscle fatigue.

In addition, it has been shown that obstructed ambulatory patients even without respiratory failure have intrinsic PEEP which is proportional to the degree of obstruction and is correlated to forced expiratory volume in 1 s (FEV_1) [27]. Furthermore, application of PEEP in mechanically ventilated COPD and asthmatic patients relieved over inflation in some of the asthmatic patients [28]. Thus, the application of externally applied PEEP to offset intrinsic PEEP might be of value in an asthmatic attack. It has been shown that application of external PEEP in a magnitude that can counterbalance intrinsic PEEP substantially reduces the work of breathing [29–31]. Asthmatic patients may also have increased physiological dead space and ventilation/perfusion mismatch [32, 33]. Externally applied PEEP may improve ventilation/perfusion mismatch and gas exchange [34]. Pressure support on ICU ventilators or its equivalent inspiratory positive airway pressure (IPAP) on an external NPPV circuit has an additional advantage of augmenting ventilation. TOKIOKA *et al.* [35] have showed that application of pressure support may decrease auto-PEEP and work of breathing in asthmatic patients. This may unload inspiratory muscles and decrease muscle fatigue.

FEV_1 and peak expiratory flow rate are used as measures of airflow obstruction. These measures can ascertain severity of disease and quantify the response to treatment. As airway obstruction worsens and work of breathing increases CO_2 production is in excess of what can be eliminated by the decreased alveolar ventilation. This has been shown to occur with a concomitant reduction of FEV_1 to <25% of predicted [36]. The mechanism by which NPPV improves FEV_1 and clinical outcome in acute asthma is not exactly understood. A combination of factors could explain at least some of the benefit.

As early as 1939 BARACH and SWENSON [37] showed that gas under positive pressure (continuous positive airway pressure (CPAP) of 7 cmH_2O) can dilate small to moderate sized bronchi. Furthermore, aerosolised bronchodilators delivered through a bi-level positive airway pressure (BiPAP) circuit resulted in improved FEV_1 and peak expiratory flow rate, suggesting that perhaps positive airway pressure could disperse the bronchodilators to more peripheral airways [38–40]. Positive pressure application may also prevent bronchospasm induced by various stimuli. Prior reports showed that methacholine and histamine induced bronchospasm could be averted by application of CPAP [41, 42]. WILSON *et al.* [43] have demonstrated that externally applied PEEP prevents exercise induced asthma. These findings strongly suggest that NPPV application may result in bronchial dilation by mechanical effect. Thus, promoting the observation that bronchial dilation decreases airway resistance, expands atelectatic regions and facilitates clearance of secretions.

EVIDENCE FOR USE OF NPPV IN ASTHMATIC ATTACKS

Only a few reports have appeared over the last 10 yrs [44–47]. Other reports dating back to the 1980s and 1990s are even scarcer, as are case series. Table 1 summarises recent reports of noninvasive ventilation in asthmatic attack. The studies were mostly performed with small number of patients and with problematic methodology [44–47].

MEDURI *et al.* [44] described a series of 17 asthmatic patients treated with NPPV during a period of 3 yrs. They used a CPAP face mask with pressure support using a ventilator (Puritan Bennett 7200 Ventilator; Puritan Bennett Co., Boulder, CO, USA) for 16±21 h. Their main finding was that NPPV improved gas exchange in status asthmaticus. A statistically significant reduction in arterial carbon dioxide tension (P_{a,CO_2}) was observed. A concomitant improvement in oxygenation was also observed, with an increase in the arterial oxygen tension (P_{a,O_2})/inspiratory oxygen fraction (F_{i,O_2}) ratio from 315±41 mmHg to 403±47 mmHg. Two (12%) out of 17 patients required intubation and there were no complications with NPPV use.

FERNANDEZ *et al.* [45] reported a 7 yr retrospective observational analysis of 33 patients with acute asthmatic attack. 22 patients received NPPV (seven CPAP and 15 NPPV with ventilators), and were compared to a group of 11 patients treated with invasive mechanical ventilation. Three (14%) out of the 22 patients in the noninvasive group were eventually intubated. On initiation of invasive and noninvasive ventilation, P_{a,CO_2} decreased similarly in both groups after 6 and 12 h of intervention. A similar improvement in P_{a,O_2} in both groups was noted as well. The results of these two reports are encouraging and reassure the feasibility of NPPV application in severe asthmatic attacks. However, both reports were a retrospective evaluation with its accompanying inherent limitations.

Our group reported a pilot study where the BiPAP circuit was applied in severe asthmatic patients who were refractory to standard medical treatment [46]. We performed a prospective randomised, sham-controlled study.

BiPAP was applied for 3 h in the emergency department *via* a dedicated BiPAP circuit (BiPAP model ST; Philips-Respironics, Murrysville, PA, USA). In the control group, a sham device was constructed by making four large holes (3 mm in diameter) in the tube connecting the apparatus and the nasal mask. Additionally, subtherapeutic inspiratory and expiratory pressures of 1 cmH_2O were used. NPPV was well tolerated in both groups and caused no complications. The use of BiPAP significantly improved lung function tests. 80% of the patients

TABLE 1 Previous reports of noninvasive positive pressure ventilation (NPPV) in asthmatic patients

First author [Ref.]	Type of study	Patients n	Study design	Mode of ventilatory support/duration of application	Outcome
MEDURI [44]	Prospective observational	17	A report of 17 episodes of status asthmaticus treated with NPPV over 3 yrs	CPAP mask with pressure support using commercial ventilator for 16 h	NPPV improved gas exchange in status asthmaticus
FERNANDEZ [45]	Retrospective observational	33	Retrospecrive comparison of 22 patients treated with NPPV *versus* 11 patients treated with invasive mechanical ventilation	CPAP with or without pressure support, using commercial ventilators for 12 h	Improved gas exchange in both groups, with the possibility of prevented endotracheal intubation in NPPV group
SOROKSKY [46]	Prospective, randomised, sham controlled	30	15 patients on BiPAP compared with sham BiPAP with standard treatment	BiPAP circuit for 3 h	Improved FEV_1 and decreased hospitalisation rate in NPPV group
SOMA [47]	Prospective randomised	44	Prospective comparison of low- and high-pressure groups to standard medical group	BiPAP circuit for 1 h	Improved FEV_1 with increasing pressure support

BiPAP: bilevel positive airway pressure; CPAP: continuous positive airway pressure; FEV_1: forced expiratory volume in 1 s.

in the BiPAP group reached the predetermined primary endpoints (an increase of at least 50% in FEV_1 compared with baseline) *versus* 20% of control patients, ($p<0.004$). The mean rise in FEV_1 was $53.5\pm23.4\%$ and $28.5\pm22.6\%$ ($p=0.006$) in the BiPAP and conventional treatment group, respectively. Hospitalisation was required for three (20%) out of 15 patients in the BiPAP group, compared with 10 (66%) out of 15 patients in the control group ($p<0.03$). Additionally, most of the patients in the BiPAP group were observed sleeping while on BiPAP (data not reported). This could suggest a relief of fatigued respiratory muscles. This was the first prospective randomised, sham-controlled study demonstrating a beneficial effect of BiPAP on lung function tests. However, a major drawback of our study was its small sample size. Nevertheless, these results are encouraging and call for a larger study.

A more recent report by SOMA *et al.* [47] has found similar results. They prospectively reported 44 patients with acute asthmatic attack who were randomised into an NPPV group (30 patients) and a control group (14 patients). Patients in the NPPV group were ventilated with BiPAP (BiPAP model ST; Philips-Respironics), and were further divided into two groups, high and low pressure. As in our study, patients in the NPPV group demonstrated an improvement in FEV_1. The mean percent change in FEV_1 significantly improved after 40 min in the high-pressure group compared with that in the control group ($p<0.0001$).

GEHLBACH *et al.* [48] reported their experience on 78 patients admitted to their ICU with status asthmaticus. 56 patients were endotracheally intubated and 22 were ventilated with NPPV. Endotracheal intubation was associated with a prolonged hospital stay and an increased rate of complications, such as barotraumas, muscle weakness, organ failure and hospital-acquired infections.

Taken together, these reports are encouraging and raise important questions. Should we initiate noninvasive ventilation (NIV) in severe asthmatic attacks on a routine basis? Is this modality suitable to all asthmatic patients? And who are the patients that would benefit the most from this intervention?

INDICATIONS AND CONTRAINDICATIONS FOR NPPV

Most exacerbations of asthma are easily controlled, and only a minority are refractory to standard treatment, with even fewer patients deteriorating to the point of respiratory failure with the need for mechanical ventilation [49]. This could explain the paucity of reports and the small number of patients in these trials.

Nevertheless, the reports that do exist clearly indicate that selected patients with severe asthmatic attacks can benefit from a carefully and closely monitored trial of NPPV. Contraindications for NPPV in respiratory failure are subject to debate. Over the last 10 yrs NPPV has gained wide acceptance for various indications. With the increased use of NPPV we gained new knowledge and experience. Therefore, we believe that under appropriate circumstances and experienced respiratory teams, NPPV use can now be extended to new diseases, such as asthma, and can be used in conditions that were previously considered as contraindications.

Table 2 describes the subgroup of patients at risk of respiratory failure who could benefit from an NPPV trial. These are usually the patients that by definition are considered to have a severe asthma attack.

The key to successful NPPV application is choosing the right patient. Patients with easily controlled disease are too easy and probably do not need any respiratory support. At the other extreme are patients with severe status asthmaticus with pending respiratory failure, and who are on the verge of endotracheal intubation.

A trial of NPPV in these patients might delay an inevitable endotracheal intubation and subject them to unnecessary risks. Therefore, these patients should be considered for endotracheal intubation sooner rather than later. Between these

TABLE 2 Risk factors and diagnostic criteria of severe asthma exacerbation

Patients at risk for respiratory failure who could benefit from NPPV trial
Diagnostic criteria of severe asthma (at least one of the following)
Use of accessory muscles
Paradoxical pulse >25 mmHg
*f*C >110 beats·min^{-1}
Respiratory rate >25–30 breaths·min^{-1}
Limited ability to speak
PEF or FEV1 <50% pred
Arterial oxygen saturation <91–92% with oxygen flow of ⩽10 L·min^{-1}
Risk factors for severe asthma exacerbation
Recent hospitalisation
Prior ICU admission with mechanical ventilation
Poor adherence to therapy
High allergen exposure

NPPV: noninvasive positive pressure ventilation; *f*C: cardiac frequency; PEF: peak expiratory flow; FEV1: forced expiratory volume in 1 s; % pred: % predicted; ICU: intensive care unit.

TABLE 3 Absolute and relative contraindications for noninvasive positive pressure ventilation (NPPV) trial

Contraindications for NPPV trial
Absolute contraindications
Need for immediate endotracheal intubation
Decreased level of consciousness
Excess respiratory secretions and risk of aspiration
Past facial surgery precluding mask fitting
Relative contraindications
Haemodynamic instability
Severe hypoxia and/or hypercapnia, $P_{a,O_2}/F_{I,O_2}$ ratio of <200 mmHg, P_{a,CO_2} >60 mmHg
Poor patient cooperation
Severe agitation
Lack of trained or experienced staff

P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension; F_{I,O_2}: inspiratory oxygen fraction.

two groups are patients with severe asthmatic attack which, if not treated aggressively, may progress to respiratory failure. These are the patients that could benefit from a closely monitored trial of NPPV.

Table 3 summarises our approach to absolute and relative contraindications of NPPV in severe asthmatic attacks. Significant hypoxia and/or hypercapnia, while previously considered a contraindication for NPPV, is now no longer considered by us as an absolute contraindication. It is our impression that under experienced personnel, and in the appropriate environment, *e.g.* admission to ICU, these patients can be safely treated with a closely monitored NPPV trial. Unstable haemodynamic patients who can not be stabilised with vasopressors or patients with worsening haemodynamic instability necessitating increasingly higher vasopressor doses should probably be intubated. However, unstable patients who can be rapidly stabilised with fluids and low doses of vasopressor could probably benefit from NPPV trial. Agitation and poor cooperation can be controlled with low doses of benzodiazepines, and as published recently with dexmedetomidine [50]. These measures may relieve agitation and promote patient cooperation, thus, preventing endotracheal intubation. However, sound clinical judgment should be applied, and these measures should be pursued only to a certain limit. Endotracheal intubation should not be delayed more than necessary.

Table 4 summarises our criteria for selecting patients who could benefit from an NPPV trial. We usually select patients with moderate disease whose FEV1 is <50% pred after at least two consecutive nebulisations with salbutamol 2.5 mg and ipratropium 0.25 mg. This allows us to screen out patients with good response to treatment who will improve rapidly. As these patients have mild disease they will probably not benefit from NPPV trial. Additional indications for NPPV use are patients with a respiratory rate >25 breaths·min^{-1}, use of accessory muscles, hypoxia with a $P_{a,O_2}/F_{I,O_2}$ ratio of ⩾200 mmHg, and hypercarbia but with a P_{a,CO_2} of ⩽60 mmHg. In addition, we recommend that an NPPV trial be carried out in an ICU environment where teams experienced in rapid endotracheal intubation are readily available.

SETTING UP VENTILATORY SUPPORT AND PATIENT VENTILATOR INTERACTION

Noninvasive ventilatory support may be applied by available ICU ventilators or by dedicated NPPV circuits. NPPV devices may offer one level of positive pressure during expirium and inspirium (CPAP), or two levels of positive pressure, in which case it would commonly be referred to as BiPAP. As there are various interpretations to the term BiPAP, its use may be confusing. The commonly used term ''BiPAP'' refers to any external device capable of delivering flow at two levels of positive pressure. As opposed to available ICU ventilators,

TABLE 4 Criteria for use of noninvasive positive pressure ventilation (NPPV)

Criteria for selecting severe asthmatic patients for NPPV trial#
Tachypnea with respiratory rate >25 breaths·min^{-1}
Tachycardia with *f*C >110 breaths·min^{-1}
Use of accessory muscles of respiration
Hypoxia with a $P_{a,O_2}/F_{I,O_2}$ ratio >200 mmHg
Hypercapnia with P_{a,CO_2} <60 mmHg
FEV1 <50% pred¶

*f*C: cardiac frequency; P_{a,O_2}: arterial oxygen tension; F_{I,O_2}: inspiratory oxygen fraction; P_{a,CO_2}: arterial carbon dioxide tension; FEV1: forced expiratory volume in 1 s; % pred: % predicted. #: in the absence of absolute contraindication the presence of at least one criterion would suffice for an NPPV trial; ¶: FEV1 <50% pred after at least two consecutive nebulisations with salbutamol 2.5 mg and ipratropium 0.25 mg.

these devices are usually light, portable and less complex than the commonly available ICU ventilator. However, BiPAP is a trademark (BiPAP model ST; Philips-Respironics) and a more suitable term would be an NIV or NPPV device.

We do not recommend the use of CPAP alone without pressure support in asthma as this mode is in effect external PEEP, which is mainly used for improving oxygenation. As CPAP has no pressure support it does not possess the added benefit of increased ventilation. Adding pressure support to CPAP increases tidal volume and helps to unload fatigued respiratory muscles [51, 52]. Therefore, we recommend the use of commercially available NPPV circuits or ICU ventilators with pressure support.

When using an NPPV circuit we recommend to start with mild to moderate support, this will enhance patient comfort and cooperation. When setting up expiratory positive airway pressure (EPAP; the equivalent to PEEP) we aim at counterbalancing auto-PEEP. We usually start with a PEEP of 3 cmH_2O and gradually increase to 5 cmH_2O. This is considered to be a mild to moderate externally applied PEEP. We do not apply >5 cmH_2O unless there is good clinical evidence of a higher auto-PEEP. Setting up IPAP (the equivalent to pressure support) is based on arbitrary values, we often start with 7 cmH_2O and titrate it to respiratory rate and patient comfort. We increase pressure support gradually to $\leqslant$15 cmH_2O until the respiratory rate is <25–30 breaths·min^{-1}. This approach was used by our group in a pilot study of NPPV in severe asthmatic attack [24]. We found it to be safe and comfortable in most patients. Furthermore, once NPPV was applied, we observed most patients sleeping with decreased tachypnea and anxiety (data not shown). We presume it is due to muscle fatigue that was alleviated with NPPV application.

CYCLING IN ICU VENTILATORS

Setting up an ICU ventilator is based on the same principle as an NPPV circuit but with some differences. When we set up PEEP the same consideration is used as with EPAP on an NPPV circuit. However, the equivalent to IPAP, *e.g.* pressure support, is different and more advanced on the ICU ventilator. Most modern ICU ventilators can deliver pressure support breaths with two types of cycling or expiratory triggers, *e.g.* time cycling or flow cycling. By setting up appropriate expiratory criteria patient comfort and synchrony with the ventilator is enhanced. In severe obstruction, airway resistance is increased, resulting in increased expiratory time constant. With the increase of expiratory time constant more time is needed for expiration [53]. The usual criterion used in most pressure support ventilators is a decrease in inspiratory flow from a peak to a threshold value (usually 25% of peak flow). Previous reports in patients with exacerbation of COPD have indicated that by increasing the flow threshold from the usual 25% of peak flow to 50% or even to 70% results in shortening of inspiratory time [54, 55], thus allowing more time for expiration. This results in reduction of delayed cycling, intrinsic PEEP and nontriggering breaths. The end result is improved patient–ventilator synchrony with a concomitant decrease in work of breathing. As lung mechanics and certain physiological parameters are similar in obstruction due to asthma and COPD [56], we suspect that the findings of the more commonly studied ventilated COPD obstructed patients could be applied to obstructed asthmatic patients as well.

A common problem with NPPV is leaks from the mask that may impair the expiratory trigger or flow cycling when inspiratory pressure support ventilation is used. In the presence of air leaks, modern ventilators do not decrease inspiratory flow due to leak compensation. As there is no decrease in flow, the ventilator will not cycle to expiration. This leads to prolonged inspiratory time and patient–ventilator asynchrony. An alternative way to flow cycling is time cycling. Limiting inspiratory time independent of air leaks allows a shorter inspiratory time. We usually set the inspiratory time to 1 to 1.3 s. However, this should be adjusted on an individual basis, and at times shorter inspiratory times are needed in severely obstructed patients. Modern ventilators allow adjustable flow cycling that, in case of leak, can also be time limited. This is probably the ideal way for expiratory trigger in noninvasive ventilation.

Therefore, in the presence of air leaks we prefer adjustable flow-cycled expiratory trigger which can be limited by time. This provides a better patient–ventilator interaction than a simple flow or time cycled expiratory trigger.

NPPV INTERFACE

We use nasal or facial masks. Due to the tight fit, facial or oro-nasal masks are more effective; however, nasal masks are preferred by some patients as this allows them to speak and clear secretions with greater ease. There is no conclusive evidence to support either interface as superior to others. Therefore, choosing between the various masks should be made on an individual basis. Some patients prefer full face masks, while others prefer oro-nasal or nasal masks. Often, the choice of the interface is influenced by local availability and local experience. Regardless of the interface, an experienced respiratory team and good patient cooperation will enhance the chances of a successful NPPV application.

POSSIBLE RISKS AND SIDE-EFFECTS OF NPPV IN ASTHMA

The use of positive pressure in asthmatic patients has been associated with increased risk of barotraumas [57]. However, acute asthma in itself carries an increased risk for pneumothorax [58].

With the use of NPPV there is always a risk of delay in endotracheal intubation. Therefore, NPPV should be applied in an ICU environment, preferably by experienced personnel. Patients who are on the verge of endotracheal intubation or with pending respiratory failure should probably be intubated without NPPV trial.

Finally, inadvertent application of extrinsic PEEP that is higher than auto-PEEP could contribute further to dynamic hyperinflation. The combination of relative hypovolaemia and excessively applied extrinsic PEEP may decreases venous return and subject the patient to the risk of haemodynamic compromise.

CONCLUSION

The benefit of NPPV is supported by evidence that NPPV may have a direct bronchodilating effect, offset intrinsic PEEP, recruit collapsed alveoli, improve ventilation/perfusion mismatch and

reduce the work of breathing. NPPV should probably be applied in select patients who have or are at risk for severe asthma attack.

No doubt, a multicenter, and perhaps an international, effort has to be conducted in order to answer some of our questions before we can conclusively recommend the routine usage of NPPV in asthma.

However, in the appropriate environment, such as an ICU with respiratory teams experienced in operating and managing patients on NIV, a cautious trial of NPPV may be tried in selected asthmatic patients.

STATEMENT OF INTEREST

None declared.

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