Chapter 5
Personalized Anesthesia for Lungs and Respiratory Tract

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Respiratory Tract and Anesthesia Related Interactions

Despite low anesthesia-specific risk, anesthesia management has important impacts on perioperative risk and perioperative outcomes. The adverse perioperative events which remain frequent, and occur in about 30% of hospital admissions, may be preventable in more than 50% of the cases, and show increasing trends according to current research results. The preoperative assessment of patients' pulmonary function is an essential part of preoperative evaluation having significant effect on decreasing post-operative pulmonary complications. This complication may be due to different pre-existing comorbidities, techniques and drugs used for anesthesia and surgical pathology (Bevacqua 2015). Patient safety should target avoidable patient harm and should be assessed, irrespective of the discipline, as carefully as any other healthcare intervention regarding their effectiveness, potential direct and indirect undesired effects, and cost-effectiveness. The NAPT study in UK showed that airway management was poorly judged in almost 3/4 of cases which can affect patient outcome (Cook et al. 2011). Each anesthetist should have a plan B besides proven technologies like fiberoptic bronchoscopy, capnography, LMA, and etc. for possible difficult airway situations. Inside the operating room, 67% of difficult intubations are noted at induction of general anesthesia, and may occur in individuals who were originally assessed as having a "normal airway". Anesthesiologists caring for the patients should also evaluate their patients regarding respiratory complications and possible risk factors. There are many scores for the prediction of respiratory complications and ARDS. The Lung Injury Prediction (LIP) Score is an alternative model initially developed for all patients, and validated in surgical critical care patients. Also, early oxygen

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saturation to fraction of inspired oxygen ratio (within 6 h of hospital admission) has been shown to be an independent indicator of ARDS development in patients at risk (Kor et al. 2014; Festic et al. 2015).

On the other way, early recognition of underlying respiratory problems and identification of causative pathogens are essential parts of preoperative management. Preoperative bedside lung ultrasound may offer additional diagnostic information about possible respiratory complications (Bass et al. 2015). Also routine approaches to reduce gastric aspiration and ventilator-associated pneumonia should be employed.

Traditional Solutions

Preoperative evaluation of each patient should be performed based on these findings: history and physical examination, previous exposure to pulmonary toxic drugs, tobacco use, airway and cardiovascular examination, diagnostic and laboratory tests like: chest X Ray, chest CT and MRI, spirometry, blood testing, carboxyhemoglobin, kidney function, arterial blood gas analysis, and exercise testing to reach the comorbid pulmonary disease (Scholes et al. 2009). Previous studies showed that there was a higher risk of pulmonary complications for patients who had a history of upper respiratory tract infection during the preoperative period, patients who underwent cardiac surgery, patients who had shortness of breath, a history of COPD, and a RI infiltration in the chest X-ray. These parameters should be examined carefully in the preoperative period, and physicians should be careful in terms of pulmonary complications that may develop during the postoperative period. There are some risk prediction scores but it is often difficult to balance these prediction scores with clinical status of the patients in the real life experience, which can lead to misprediction of the patients' status and postoperative complications (Johnson et al. 2017). Previous studies showed that checklists, team work and communication in operating room and compliance with safety measures, could decrease all perioperative anesthesia-related complications (Wacker and Staender 2014). Each anesthesiologist should be familiar to the difficult airway algorithm. Also surgical airway should be taken into consideration early in the event of a 'can't ventilate can't intubate' scenario and requires active communication between the anesthesiologists and the surgeons. From a pharmacological standpoint, the introduction of sugammadex for reversal of neuromuscular blockades may become an adjunct to the difficult airway algorithm. Sugammadex actively binds to rocuronium or vecuronium, eliminating the paralysis induced by those agents. Although it has been used in the clinical event of inability to intubate, its usefulness for 'can't intubate can't ventilate' has been called into question due to the time it takes to draw up, administer, circulate and have an effect (Steadman et al. 2017).

Personalized Medicine Solution

The concept of "one size fit all" does not work well for medical therapies nowadays. For many years the aim of physicians has been to provide an effective treatment and predict an appropriate outcome for their treatment. But in practice patients showed different responses for a single or combination of drugs (Cesuroglu et al. 2016). The solution for preventing these ineffective treatments, serious adverse effects, different morbidities and mortality can lie in the emerging field of personalized medicine. Personalized medicine is the concept of tailoring pharmacotherapy to an individual patient based on their predicted response to that therapy. Its application to perioperative medicine is novel, and has a great potential for growth. Despite recent advances in the field of personalized medicine, this approach has not yet been widely developed in the preoperative medicine. But personalized medicine can play an important role in the preoperative period (Ginsburg and Phillips 2018). General anesthesia is a state of unconsciousness, amnesia, analgesia and akinesia induced with some drugs like opioids, muscle relaxants, hypnotic/sedative agents and antiemetics. Clinical and genetic factors like patient's age, ethnicity, genetic mutation and comorbidities can change the efficacy of these drugs. Much progress has been made in omics research following the completion of the Human Genome Project. This comprehensive analysis introduced the bioinformatics which is contributed to the clinical practice of anesthesiology. Patients' genomes show genetic variations and may predict the sensitivity to anesthetics and analgesics, incidence of adverse effects, and intensity of postsurgical pain. In addition, novel epigenome researches may explain why environments change the phenotypes of clinical anesthesia.

Genomics/Pharmacogenomics

The preoperative period represents a good example of using personalized medicine in our practice in both operating room and intensive care unit. There is interindividual variability in patients' response to different stresses like hemodynamic changes, surgical injury, vascular cannulation, extracorporeal circulation, intraaortic balloon counterpulsation, mechanical ventilation, organ resection and donation, transfusion and anesthetic agents (Saba et al. 2017a, b). For many years we thought that this variability is related to different parameters like age, nutritional status, comorbidities and etc. We now know that genomic variation contributes to most of these differences in patients' response. Pharmacogenomics focuses on identifying genetic variants which modulate pharmacokinetic and pharmakodynamic of the drugs. The earliest report of pharmacogenomics goes back to 510 BC, Pythagoras reported the development of hemolytic anemia in patients who ate fava bean, which is now related to G6PD deficiency (Relling and Evans 2015). In 1950, Friedrich

Table 5.1 Important considerations related to successful clinical implementation of pharmacogenomics

Clinical scenario	Computer technology	Socioeconomics
Evaluation of effectiveness	Storage of pharmacogenomics data	Cost
Valid therapeutic targets	Electronic health record integration	Reimbursement
Improvement of assays	Thoughtful software design	Physician use
		Education
		Ethics

Vogel used the term "pharmacogenetics" for the first time (Relling and Evans 2015). With increasing evidence from literature, genomic variations can significantly modulate the risk of anesthesia and operative related anesthesia, so preoperative genomics provides innovative functional approaches and techniques to define the individualized responses to anesthesia and operation (Linares et al. 2014, 2015). Hence preoperative genomics has gained good results but its implementation in clinical practice is very slow. To solve this problem we need more evidence from high quality clinical studies for preoperative genomics, newer point of care techniques and easy to access methods for patient care and settings to adjust it to regular clinical practice (Gabriel et al. 2017). Genomic study should be started in surgeons' clinic or anesthesia clinic prior to the scheduled surgery, so healthcare providers can modulate the potential genetic risks to specific drugs. Based on recent studies, implementation of this technique to ERAS protocols will further facilitate more widespread adoption (Helander et al. 2017; Modesitt et al. 2016). Important considerations related to successful clinical implementation of pharmacogenomics were shown in Table 5.1.

Prolonged Apnea After Succinylcholine Administration

Dr. Werenr Kalow introduced pseudocholine esterase deficiency for the first time (Jones 2011). After that he developed a method to detect the so called "atypical pseudocholine esterase" activity by dibucaine among normal variants, heterozygotes, and homozygotes, which remains the standard of detection of this disease today (Kalow and Genest 1957). Nowadays we are aware of at least 10 different polymorphisms of pseudocholine esterase with K and A variants as the most common types. The K type leads to decreased production of the enzyme but the A type results in the dibucaine-resistant version (La Du et al. 1990).

Malignant Hyperthermia

The exact mechanism of malignant hyperthermia (MH) is still unknown. Muscle rigidity after succinylcholine is an early warning sign which may suggest a skeletal muscle abnormality. A mutation in ryanodine receptor was proposed as a mediator

for malignant hyperthermia (MacLennan et al. 1990). Now we know more than 200 ryanodine gene variants which only about 20 are considered to influence the patients' susceptibility to MH (Davis and Brandom 2009).

Opioid Analgesics Metabolized by CYP2D6

Codeine is a prodrug which is metabolized into morphine by CYP2D6. Some patients who have two dysfunctional copies of this gene are unlikely to convert codeine into morphine and therefore are unlikely to achieve analgesic effects. Some patients have two functional copies of the gene which are able to completely metabolize codeine (Palmer et al. 2005). These individuals are at increased risk of respiratory dysfunction after anesthesia even after standard doses of codeine. If an individual is known to be an ultra-rapid metabolizer, opioid drugs which rely on CYP2D6 like codeine, tramadol, hydrocodone and oxycodone are not recommended for analgesia and other drugs that their metabolism is not dependent on CYP2D6, like morphine or nonopioid analgesics should be considered (CPIC n.d.). It seems that ethnicity has a great impact on the incidence of the CYP2D6 polymorphism, as Ethiopians, Arabs, North Africans have nearly a 30% incidence of ultra-rapid metabolizer gene (Mizutani 2003).

Nitrous Oxide Toxicity

Prolong exposure to N_2O can be associated with megaloblastic anemia, agranulocytosis and neuropathy. Neuropathy can be seen with short-term exposure to N_2O in children with variants in the gene encoding 5,10 methylene tetrahydrofolte reductase (MTHFR). So, N_2O should not be administered to patients with MTHFR deficiency or a familial history of this condition. Previous studies showed raised plasma homocysteine concentrations after 2 h nitrous oxide exposure in patients homozygous for either of the two common variants in the MTHFR gene (Selzer et al. 2003). The clinical importance of these observations is not known, but if transiently increased plasma homocysteine concentrations is shown to be associated with worse clinical outcomes, physicians should check genotyping of MTHFR variants preoperatively to perform safe personalized anesthesia (Hogan 2008).

Intraoperative Respiratory Complications

Anesthesia has several respiratory complications which should be considered during the operation. Some of these complications are atelectasis due to reduced functional residual capacity, high Fio_2 and positioning, increasing closing volume and decreasing minute ventilation and increased alveolar dead space ventilation.

Traditionally anesthesiologists try to reduce these complications by applying positive end expiratory pressure, higher respiratory rate with low tidal volume strategy, recruitment maneuvers, optimized use of neuromuscular blocking drugs with monitoring the depth of block, and head elevation during the intraoperative period. Following we describe pharmacogenetics of some drugs that are used during anesthesia and it seems logical that having information on patients before surgery would be a valuable tool to anesthesiologists because it can allow effective and ideal management of anesthesia in each patient. Different drugs used during anesthesia may have different effects on respiratory function based on genetic variations as the followings:

Morphine

Is frequently used during anesthesia for acute and chronic pain control. OPRM1 is an important gene in pharmacogenetic properties of morphine. Previous studies showed that patients with OPRM1 rs 1,799,971 variation had the lowest morphine consumption and pain scores but a high incidence of nausea (Sia et al. 2008). Previous studies showed that patients with ABCB1 rs 1,128,503 and rs 1,045,642T alleles required less morphine for acute postoperative pain control (Bastami et al. 2014). Also mutation of ABCB1 rs 9,282,564 gene can result in respiratory depression with morphine (Sadhasivam et al. 2015).

Finally, due to the small effect size and unconfined reproducible outcomes of the current studies, OPRM1 and ABCB1 may not serve as an ideal predictive biomarkers and more strong evidences are required to guide morphine use in the clinic, based on a patient's genetic profile (Stamer et al. 2013a).

Codeine

Based on the 2014 CPIC guidelines for cytochrome P450 2D6 genotype and codeine therapy, *CYP2D6* extensive metabolizers and intermediate metabolizers could use label-recommended dosing but ultra-rapid metabolizers and poor metabolizers are recommended to use alternative analgesics rather than codeine (Crews et al. 2014).

Fentanyl

*CYP3A5*1* is the only functional allele, individuals with at least one **1* allele are expressers while others are nonexpressors (Tanaka et al. 2014) but those patients who had rs2076222 C allele showed lower sensitivity to fentanyl (Mieda et al. 2016). So knowing this information help physicians to decrease respiratory complications.

Tramadol

Tramadol is metabolized by CYP2D6 to its main active metabolite O-desmethyltramadol and current guidelines recommend that ultra-rapid metabolizers should either reduce the dose by 30% or use another drug. Intermediate metabolizers should be aware of reduced efficacy and resistant individuals should use alternate drugs. Although these clinical therapeutic recommendations cannot achieve personalized precision medicine at present, the utility of *CYP2D6* genotype to tramadol dosing is certain (Dean 2015).

Oxycodone

Oxycodone can treat multiple types of pain and is often a substitute for other opioids when they are ineffective. The recommendations for oxycodone are similar to the guideline for tramadol and codeine, so the alternative drug should not contain tramadol or codeine which is metabolized by CYP2D6 (Stamer et al. 2013b).

Methadone

Methadone is generally used in addicted patients and recent studies showed that CYP2B6 can be a key dose-guiding element regarding its effect on different individuals (Yang et al. 2016).

Aspirin

Differences in *UGT1A6* and *CYP2C9* have been implicated in aspirin resistance and the safety of antiplatelet doses. Also other genes such as *GP6* and *PEAR1* were studied more extensively in relation to this function (Yiannakopoulou 2013).

Ibuprofen

Recent studies have shown that CYP2C8*39 (increased metabolism of *R*-ibuprofen), CYP2C9*2 and CYP2C9*3 (decreased clearance of ibuprofen) are important alleles in the metabolism of ibuprofen and all these alleles lead to a reduced activity of CYP enzymes (López-Rodríguez et al. 2008).

Barbiturates

More evidence is needed to elucidate the mechanism of this drug and the genes that may influence its efficacy however these drugs are largely replaced by benzodiazepines.

Midazolam/Diazepam

Midazolam is metabolized by CYP3A in liver and the results of a study in 24 Asian patients with advanced stage gastrointestinal cancer showed that *CYP3A5*3* carriers had 22% lower typical clearance of midazolam than noncarriers. Also, *CYP3A4*22* T allele was associated with reduced oral clearance of midazolam in non-*CYP3A5*3* carriers (De Jonge et al. 2015). Choy et al. in their study showed that polymorphism of rs4263535 (187 + 3553A > G) in *GABRA1* intron 4 was associated with more sedation induced by midazolam and patients with rs4263535 required a less dose of midazolam (Choi et al. 2015).

Previous studies showed that CYP2C19 polymorphism can affect diazepam pharmacokinetic. But a newly performed study in south Indians showed no significant correlation between CYP2C19 and diazepam kinetic (Jose et al. 2016).

Propofol

Propofol is metabolized by CYP2B6 in the liver, but nearly 70% of propofol undergoes *O*-glucuronidation by UGT1A9 (Mikstacki et al. 2013a). However, both SNPs of CYP2B6 and UGT1A9 showed no significant effects related to propofol metabolism in a previous study (Loryan et al. 2012), so we need more evidence to show the exact effect of these variations in the kinetic of propofol.

Volatile Anesthetics

CYP2E1 plays an important role in the metabolism of these agents and also other genes such as *MC1R* are also related with the anesthetic effect of volatile anesthetics (Mikstacki et al. 2013b). Different studies showed that the serum α-GST can be used as a marker of hepatic condition, especially for sevoflurane (Cohen et al. 2012).

Dexmedetomidine

Although data regarding the metabolism of dexmedetomidine is limited, an important route of metabolism is mediated essentially by CYP2A6 (Kohli et al. 2012). But a few studies showed that patients with *ADRA2A* rs1800544 (-1291C > G) G allele had higher Bispectral Index and Ramsay Sedation Scores indicating a prolonged time to falling asleep; this should be considered when using this drug as a sedative (Yağar et al. 2011).

Neuromuscular Blocking Agents

Succinylcholine is hydrolyzed by BChE in plasma; based on previous trials, *BCHE*FS126* can silence the enzyme function and cause prolonged duration of neuromuscular blockade (Delacour et al. 2014).Also, seven novel mutations were found in *BCHE* (I373T, G467S, W518R, L184S, V421A, M462I and R577H) that were associated with prolonged effect of succinylcholine or mivacurium (Wichmann et al. 2016).

Antiemetics

Postoperative nausea and vomiting (PONV) is one of the most common complications in clinical anesthesia, and receptors such as dopamine, opioid and 5-HT3 receptors are related to the emetic center. The CPIC guideline published in 2016 summarized that patients with *CYP2D6* UM are recommended to select an alternative drug to ondansetron, which is not predominantly metabolized by CYP2D6 (Bell et al. 2017). Previous studies showed that polymorphisms of *ABCB1* can affect the expression and function of P-gp which are associated with ondansetron efficacy (He et al. 2014), but more recent studies showed that *ABCB1* might not serve as a suitable predictive biomarker in drug treatment (Bruhn and Cascorbi 2014). *SLCO1B1*, *ABCB1* and *CHRNA1* gene polymorphisms in Chinese patients combined with ondansetron administration, *ABCB1* rs1128503 TT, and *SLCO1B1* rs2306283 (A388G) AG/GG patients, were shown to have a prolonged clinical duration and recovery time (Mei et al. 2015). Like ondansetron, the *CYP2D6* genotype is significantly associated with the effects of tropisetron and this genetic factor should be considered with regards to the dosage of tropisetron, as recommended by the CPIC guideline (Bell et al. 2017).

Vasopressors

Zhang et al. showed that the EDN2 gene has a strong biological relevance to vasoconstriction by binding to endothelin type A receptors on arterial smooth muscle cells but we need further trials to show the clinical effectiveness and the importance of this finding (Zhang et al. 2019).

Pharmacogenetic studies of anesthetic drugs will help physicians to understand their genetic contribution and to decrease their complications. On the other hand, the different results because of the heterogeneous and small sample sizes of these trials, makes the implementation of pharmacogenetics difficult in the field of anesthesia.

Personalized Medicine in Interstitial Lung Disease

During the past years molecular and genetic approaches regarding diagnosis and management of interstitial lung disease (ILD) improved dramatically. The importance of personalized medicine in ILD should be established and more projects are needed to prospectively validate the available data. One could argue that the cost of personalized in ILD could be very high, especially in times when research resources are limited. However, the validation and use of reliable peripheral blood biomarkers in ILD could counterbalance this argument, with a substantial potential for reduction in healthcare cost by decreasing the number of lung biopsies for diagnosis and CT scans for disease progression monitoring and also a decrease in ICU length of stay. Before implementation of precision medicine we should answer these questions: identify unmet need, define intended use population, biomarker discovery, analytical validation, clinical validation, Establish broad clinical utility and enable widespread use.

Interstitial Pulmonary Fibrosis

Although environmental risk factors have long been known in IPF, genetic risk factors have recently been established. Regarding heterogeneity in IPF natural history, a genome wide investigation aimed at identifying single nucleotide polymorphism linked to IPF prognosis would greatly increase our ability to incorporate genetics into prognostic scores, diagnostic and therapeutic models (Herazo-Maya et al. 2013).

Sarcoidosis

Because of the lack of diagnostic gold standard for sarcoidosis, lack of standard protocol for management, highly variable mode of presentation and poor correlation between disease activity and severity development and applicability of biomarkers remains problematic.

Pulmonary Hypertension

Recent trials have shown the application of molecular phenotyping in diagnosis and management of PAH (Sweatt et al. 2019a). We should intend to expand the cytokine and chemokine panel, broadly assess the circulating immune cell landscape, examine transcriptomic profiles to ascertain differentially expressed transcripts and enriched biological pathways, and analyze histopathology in explanted lungs from transplant recipients (Hollander et al. 2017). In the future invention of point-of-care test that feasibly stratifies immune endotypes and guides the selection of precision immune-targeting therapies will help to management of this disease. Application of machine learning algorithms to these types of datasets will allow physicians to be exemplars of an optimal system that is facile enough to be utilized for prevention, diagnostics, or therapeutics. This evolving use of precision medicine to understand and define subphenotypes of patients with pulmonary hypertension, therefore, has the potential to improve health, support prevention strategies, and select interventions with a high probability of successful outcome (Sweatt et al. 2019b).

Personalized Medicine for Chronic Obstructive Lung Disease and Asthma

Nonresponse to pharmacologic and non-pharmacologic treatments is common, and many patients have refractory symptoms. Thus, there is an ongoing urgency for a more targeted and holistic management of the disease, incorporating the basic principles of P4 medicine (predictive, preventive, personalized, and participatory). Currently Strategies to personalize the treatment of exacerbations are not available but increased understanding of individual genetic variants modulating the immune response involved in exacerbation susceptibility and response to therapy may improve personalized exacerbation management in future patients in perioperative management of these patients (Ishii et al. 2017). A multidisciplinary systems medicine approach may reveal the multilevel complexity of COPD and fill current gaps in optimization of therapy for persons at risk and those with established airflow limitation. Precise clinical "personalised" assessment, with a special focus on understanding the clinical problem, addressing extra-pulmonary morbidity and managing behavioural challenges, such as non-adherence to inhaled steroid treatment, is just as critical to precision medicine in airways disease as targeting the right drug to the right patient.

The relationship between lung microbial environments and COPD exacerbations can be targeted in precision medicine treatments for frequent-exacerbator patients. During consideration for implementation of personalized medicine for patients with OLD, we should consider individual barriers like: physical limitation, psychosocial disease, motivation and attitude *vs.* individual enablers like selfregulation, achievements, autonomus motivation and controlled motivation (Wouters et al. 2018).

For patients with OLD in perioperative period especially before the anesthesia targeting to stable airway situation can result in better anesthesia outcome and decreased postoperative complications.so personalized medicine help to

understanding the underlying pathobiology both for defining disease endotypes and for appropriately targeting therapies to individual patients.

Sleep Apnea and Personalized Medicine

Recently performed studies showed that the "excessively sleepy" subtype was associated with a more than threefold increased risk of prevalent HF compared with each of the other subtypes. Symptom subtype was also associated with incident CVD, coronary heart disease which is important in implementation of therapeutic interventions (Sánchez-de-la-Torre et al. 2015). So, exploring the relationship between excessive sleepiness, physiologic phenotyping and biological markers of oxidative stress and inflammation may also yield important insights. Recently many studies performed in adults and children with OSA using proteomics, studies on miRNA in patients with OSA and resistant hypertension, the application of system biology to genetic studies of OSA and studies on visceral fat transcriptome to assess the molecular basis of the interaction between OSA and obesity (Sánchez-de-la-Torre et al. 2015). Based on this approach we can use anatomical interventions, targeted combination therapy (oxygen, upper airway muscle training, hypoglossal nerve stimulation, drugs to increase upper airway muscle activity, loop gain or increase arousal threshold, mandibular advancement splint) based on patients characteristic (Bonsignore et al. 2017).

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Electronic Health Records

EHRs can store much more information than paper records, and therefore appropriate care is required to keep the information concise to avoid hiding important data among the extraneous patient history. Security should be taken seriously, as electronic forms are more susceptible to security attacks. Creating a partnership between investigators to integrate EHR analysis with clinical research and biomarker identification, multi OMICs analysis, to better understand basic mechanisms of disease could create a powerful approach to identify new treatment options for patients with lung disease (Sulmasy et al. 2017).

Microbiomics and Personalized Anesthesia

Human would basically have two genomes: the human genome and the microbiome; therefore, the changes in the microbial population of the microbiota would result in the manifestation of dysbiosis and, therefore, in the subsequent onset or

flare-up of diseases (Eckerle et al. 2017). Previous studies showed that anesthesia and surgery can induce dysbiosis which is an important risk factor for the pathophysiology of the three most common causes of readmission after gastrointestinal surgery: surgical site infections, ileus, and anastomotic leak (Angulo et al. 2019). Also there are so many studies showed that gut microbiota can contribute to development of ARDS and obstructive lung disease. So considering microbiomics in perioperative medicine not only can improve our anesthesia situation but also could decrease the different postoperative complications.

It is accepted that gut microbiota plays a critical role in the development of pain. Although our understanding of the role of gut microbiota in pain is still in its early stages, emerging evidence suggests that dysregulation of gut microbiota participates in visceral pain, inflammatory pain, neuropathic pain, migraine, and opioid tolerance (Fischbach 2018). So, modulation of gut microbiota by diet and pharmabiotic intervention offers a promising approach to the management of chronic pain in perioperative medicine and toward targeted anesthesia.

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