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Acquired Methemoglobinemia from Local Anesthetics Used for Airways: Incidence, Risk Factors, and Management

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ABSTRACT

Background: Acquired methemoglobinemia from topical/local anesthetics used for airway procedures is uncommon but clinically important. Risk appears highest with benzocaine sprays during transesophageal echocardiography (TEE) or bronchoscopy, whereas standard-dose lidocaine typically yields only minor, asymptomatic methemoglobin (MetHb) changes.

Methods: We systematically searched PubMed (to June 2025), screened records in duplicate, and included observational clinical trials or cohort/case-control studies evaluating airway topical/local anesthetics and methemoglobinemia. Data were extracted in duplicate and synthesized narratively without meta-analysis due to heterogeneity in designs, exposures, and outcome definitions.

Results: Nine observational studies met eligibility (0 randomized trials). Across mixed procedure cohorts, incidence was low (0.035% overall; 33/94,694 procedures), with higher procedure-specific rates for TEE (0.250%) and bronchoscopy (0.160). A large TEE program reported benzocaine-associated incidence 0.067% (95% CI 0.040-0.100). Inpatient status markedly increased risk (13.7 vs 0.14 per 10,000 for inpatients vs outpatients). Prospective studies of lidocaine topicalization/infiltration showed trivial mean MetHb shifts (e.g., =0.5% to 0.6%) without clinical toxicity.

Conclusions: Airway topical/local anesthetic-associated methemoglobinemia is rare and concentrated around benzocaine spray in medically complex inpatients. Routine lidocaine use at standard doses demonstrated minimal clinical risk. Early recognition with co-oximetry and timely methylene blue remain central to excellent outcomes, and risk can be minimized through agent selection and dosing discipline.

Keywords: Methemoglobinemia, Airway management, Anesthetics local, Benzocaine, Lidocaine, Transesophageal echocardiography

INTRODUCTION

Methemoglobinemia is a rare but potentially life-threatening disorder in which hemoglobin's iron is oxidized from Fe^{2+} to Fe^{3+}, rendering it unable to bind oxygen [1]. Under normal physiology, ≥98% of hemoglobin iron is the functional Fe^{2+} form; even small increases in methemoglobin can impair oxygen delivery. Acquired methemoglobinemia is most often due to exposure to oxidant drugs or chemicals [1]. In particular, commonly used topical/local anesthetics - such as benzocaine, lidocaine, and prilocaine - can induce methemoglobin formation when applied to the oropharynx or airway mucosa [1]. These agents are widely used in airway-related procedures (e.g. bronchoscopy, intubation, upper endoscopy, transesophageal echocardiography) to numb mucosa or suppress the gag reflex [1]. Methemoglobinemia typically presents with cyanosis, brown ("chocolate-colored") blood, and low pulse oximetry despite normal PaO_2 [1].

Symptoms (e.g. headache, dyspnea, tachycardia, confusion) correlate with methemoglobin level: for example, levels of 20-50% often cause anxiety, tachycardia, and dyspnea, while levels >50% can produce stupor, arrhythmias or death [1,2]. Complications of untreated severe methemoglobinemia include hypoxic encephalopathy, myocardial infarction, and death [2]. Because methemoglobin cannot carry oxygen and also shifts the oxygen-dissociation curve leftward, the resulting tissue hypoxia can be profound even in the presence of normal arterial oxygen tension.

Anesthesia providers have recognized methemoglobinemia as a rare complication of peri-procedural topical anesthesia. In 2008 Kwok et al reported a case of methemoglobinemia during bronchoscopy after combined benzocaine and lidocaine use [3]; that report notes that "methemoglobinemia is an uncommon but potentially fatal hemoglobinopathy" often seen when topical anesthetics are used during bronchoscopy, laryngoscopy, or endoscopy [3]. Indeed, virtually any potent topical anesthetic can trigger the condition: benzocaine (ester class) is well known for this risk, while lidocaine and prilocaine (amides) have also been implicated. A review of 242 reported cases of local anesthetic-induced methemoglobinemia found that benzocaine was the culprit in the majority, and cautioned that even a single spray of benzocaine can induce clinically significant methemoglobinemia [2]. Because topical sprays can deliver large doses rapidly, they are especially hazardous. In short, any use of potent or high-dose local anesthetic on airway mucosa creates a risk for this “silent” hypoxia that clinicians must know.

The published literature on airway-related methemoglobinemia is dominated by case reports and small series, with few large-scale studies. Chowdhary et al’s seminal case-control study (2001-2011) is one of the few large series: they identified 33 methemoglobinemia cases out of 94,694 airway procedures (incidence 0.035%) [1]. In that series the highest procedure-specific prevalence rates were seen in bronchoscopy (0.160%) and transesophageal echocardiography (0.250%), compared to only 0.005% in routine upper endoscopy [4]. For example, 9 of 5,558 bronchoscopies (0.160%) and 16 of 6,436 TEEs (0.250%) were complicated by methemoglobinemia [4]. Inpatients were far more likely than outpatients to develop methemoglobinemia (13.7 vs 0.14 cases per 10,000 procedures, $p<0.001$) [1], suggesting unmeasured patient or practice factors. This study also found that benzocaine-containing sprays were disproportionately represented in the case group (24 of 31 cases vs 109 of 205 controls, $p=0.01$) [4], supporting benzocaine’s high risk. Otherwise, differences in demographics (age, sex) were not significant, though cases tended to have more cardiovascular or pulmonary comorbidities [4]. In sum, retrospective data from a large U.S. center indicate that methemoglobinemia after airway anesthetics is rare (<0.05%) but does occur, especially with certain procedures and in hospitalized patients [1,4].Beyond that, much of the evidence is anecdotal. A systematic review of 87 published cases (1980-2020) found that most anesthetic-related methemoglobinemia episodes happened in the peri-procedural setting [5]. Interestingly, in that review 52% of acquired methemoglobinemia cases involved dapsone or cocaine-based anesthetics (often dermatologic or ENT use), reflecting a different context [5]. However, among cases due to local anesthetics, benzocaine was the culprit in the majority; lidocaine and prilocaine accounted for far fewer.

In the reviewed cases, 82% presented with cyanosis and about 60% had SpO_2 below 90% [5]. Methylene blue (MB) was used in 71% of cases [5], reflecting the need for specific therapy. These compilations underscore that while benzocaine is the prototypical cause, any strong oxidizing topical agent can cause methemoglobinemia, and that clinicians should watch for it in airway procedures. No recent prospective cohort studies were found, highlighting how most data come from retrospective analyses and case series.Overall incidence of methemoglobinemia from airway anesthetics is extremely low, but quantifying the global burden is difficult. Most published series come from high-income countries. In the United States, regulatory agencies have documented hundreds of cases over decades. For example, a 2018 FDA safety announcement noted that >400 cases of benzocaine-associated methemoglobinemia (mostly pediatric teething products) have been reported to FDA or in the literature since 1971 [6]. In that analysis (2009-2017) there were 119 reported cases requiring treatment, including 4 deaths (one in an infant) [6].

Earlier FDA reports (1990s-2000s) had identified 132 benzocaine-related cases with 2 fatalities [7]. In other regions, formal data are scarce. European databases have few specific reports; there is no global registry of medication-induced methemoglobinemia. Case reports have appeared from many countries but mostly as isolated incidents. Importantly, many affected patients survive with proper treatment, but fatalities do occur: benzocaine-associated deaths have been documented (e.g. 7 deaths among 319 cases in one U.S. report) [6]. In summary, the absolute worldwide burden of anesthesia-related methemoglobinemia is low (likely well under 1 per 10,000 uses of topical anesthetic), but it is serious when it occurs.For Saudi Arabia specifically, we found no population-based studies. Use of topical anesthetic sprays and gels is common in Saudi airway practice (as globally), but reporting of adverse events is sporadic. A search did not reveal any Saudi case series or pharmacovigilance reports on this topic. Thus, local incidence is unknown; by default one assumes similar rates to other countries. Saudi clinicians should remain vigilant given the worldwide experience. The broader global picture is that methemoglobinemia from airway anesthetics is a rare complication but one highlighted in safety communications; hence, regulators now carry boxed warnings for these agents [6,8].

Multiple risk factors have been identified for anesthetic-induced methemoglobinemia. Procedural factors include the type and dose of anesthetic: benzocaine spray, especially repeated application, is the strongest culprit. One lab study confirmed that benzocaine produces significantly more methemoglobin than lidocaine at equivalent conditions [6]. Prilocaine (commonly used in infants/dentistry) is also highly prone to cause methemoglobinemia at high doses (e.g. >400-600 mg) [9]. Sprays are riskier than gels or lozenges

because they often deliver larger doses quickly. Case reports suggest even one or two sprays of benzocaine can precipitate toxicity [2]. Concomitant use of multiple oxidizing agents can additively increase risk (e.g. using both lidocaine and benzocaine in one procedure) [3].Patient-related factors include age and comorbidities. Infants (especially under 4-6 months) have low levels of the NADH reductase enzyme and fetalhemoglobin, making them unusually susceptible [6,9]. Elderly patients have diminished reductive capacity. Underlying cardiorespiratory disease (asthma, COPD, heart failure) worsens the impact of any hypoxia [6,10].

Genetic factors predispose: G6PD deficiency or hemoglobin M variants reduce the ability to reduce methemoglobin, increasing both the likelihood and severity of an episode [6,9]. Environmental exposures (nitrate-rich diet or water, dapsone, sulfonamides) can also contribute by raising baseline methemoglobin levels, though these are usually discussed with systemic drugs. In one prospective U.S. study, having any pulmonary or cardiac comorbidity was significantly more common among methemoglobinemia cases than matched controls [4]. Thus, both anesthetic and host factors modulate risk.The primary clinical outcome is hypoxia: methemoglobinemia can cause refractory into hypoxemia and lactic acidosis if not treated. Death is rare but documented (e.g. 2%-5% of reported benzocaine cases [7,6]). Neurologic injury from sustained hypoxia has been reported anecdotally. In the acute setting, all patients with methemoglobinemia should receive supplemental oxygen and, if methemoglobin exceeds about 30% or if they are symptomatic, methylene blue therapy [1,5]. Intravenous methylene blue acts as a cofactor to reduce methemoglobin and is typically effective within minutes. In reviewed cases, 71% required methylene blue [5]. Without timely treatment, oxygen delivery to tissues remains compromised, potentially leading to organ damage. After treatment, patients usually recover fully if no other complications intervene.

Several quantitative risk estimates are notable. In Chowdhary's case-control analysis, inpatient status had a dramatic effect: the in-hospital incidence was roughly 13.7 per 10,000 procedures versus only 0.14 per 10,000 in the outpatient setting ($p<0.001$) [1]. Underlying pulmonary disease also appeared to increase odds of methemoglobinemia (cases 45.5% vs controls 17.4%, $p<0.001$) [4]. While we found no meta-analysis giving a pooled OR, these figures suggest relative risks on the order of 10-100× for certain factors (inpatient care, high-dose benzocaine, etc.). For context, standard practice guidelines now warn that patients with any cardiac or respiratory compromise, smokers, or the very young/old carry higher risk [6,10]. Overall, benzocaine sprays have the highest per-dose risk of any commonly used topical anesthetic, consistent with both clinical series and regulatory findings [6,2].

Despite recognition of the problem in case series and warnings, several knowledge gaps remain. First, no systematic review has focused specifically on airway-related anesthetics; existing syntheses lump in all causes of acquired methemoglobinemia. Second, most studies are retrospective and context-specific (e.g. gastroenterology units), limiting generalizability. Third, little is known about incidence in special populations (e.g. pediatrics) or techniques (e.g. spray vs swab). Finally, regional data (e.g. Saudi Arabia or Middle East) are essentially absent, so it is unclear how global epidemiology translates locally. This scarcity of high-quality evidence makes risk estimation and management protocols inconsistent.To address these gaps, we propose a systematic review. Our aim is to synthesize the evidence on incidence, risk factors, and management of acquired methemoglobinemia associated with topical or local anesthetics used in airway procedures. Specifically, we will aggregate data from all available studies (case reports, series, and retrospective analyses) to estimate the global incidence rate, identify patient and procedural risk factors (with quantitative measures where available), and summarize clinical outcomes and treatments. This review will provide a comprehensive picture of this rare but serious complication, guiding safer use of airway anesthetics.

METHODS

We conducted a systematic literature search using PubMed from database inception through 30 June 2025, adhering to PRISMA 2020 guidance. The strategy targeted studies reporting incidence, risk factors, clinical features, or management of acquired methemoglobinemia caused by topical or local anesthetics used during airway-related procedures such as transesophageal echocardiography, bronchoscopy, endotracheal intubation, and laryngoscopy. The exact PubMed query was: ("Methemoglobinemia"[Mesh] OR "Methemoglobinemia"[tiab]) AND ("Anesthetics, Local"[Mesh] OR "Topical Anesthetics"[tiab] OR "Lidocaine"[tiab] OR "Benzocaine"[tiab] OR "Prilocaine"[tiab]) AND ("Airway Management"[Mesh] OR "Airway"[tiab] OR "Bronchoscopy"[tiab] OR "Transesophageal Echocardiography"[tiab] OR "Endotracheal Intubation"[tiab] OR "Laryngoscopy"[tiab]). Results were limited to human studies published in English. No design filters were applied to capture case reports, series, observational studies, and trials. Secondary sources (Scopus and targeted citation chasing in Google Scholar) were consulted to identify additional records.All records were imported into EndNote X9 for de-duplication.

Two reviewers independently screened titles and abstracts against prespecified eligibility criteria: human participants, airway-related procedure, exposure to a topical or local anesthetic applied to airway mucosa, and a

clinical diagnosis of acquired methemoglobinemia. Potentially eligible reports proceeded to full-text assessment using the same criteria, with the additional requirement that the procedure type and anesthetic agent(s) were explicitly stated. Disagreements were resolved by consensus with recourse to a third reviewer when needed. Inter-reviewer agreement was evaluated with Cohen's kappa on a calibration set after training; the observed agreement exceeded the prespecified threshold for excellent concordance ($\kappa > 0.80$; κ = for the calibration sample pending final adjudication).A standardized extraction form (Microsoft Excel) was developed and pilot-tested on five studies, then refined for clarity and field definitions. Two reviewers independently extracted study characteristics (year, country, design, sample size), population descriptors (age, sex, comorbidities), procedural details (bronchoscopy, transesophageal echocardiography, intubation, laryngoscopy), anesthetic exposures (agent, concentration, dose, route), diagnostic confirmation (co-oximetry, methemoglobin percentage), management (oxygen, methylene blue, ascorbic acid, exchange transfusion, hyperbaric oxygen), and clinical outcomes (need for intensive care, length of stay, mortality). Conflicts were reconciled by discussion and, when required, third-party adjudication. Extracted tables were cross-checked for internal consistency before synthesis. A formal risk-of-bias assessment was not performed because the evidence base was expected to be dominated by case reports and case series and because no statistical pooling was planned. Instead, we recorded key methodological limitations narratively for each study, including selection processes, exposure ascertainment (agent identity, dose, delivery method), diagnostic verification (use of co-oximetry), and outcome completeness. These considerations informed the interpretation of results in the synthesis without producing numerical quality scores.

Given the anticipated heterogeneity in designs, populations, exposure regimens, and outcome definitions, we did not conduct meta-analysis or calculate quantitative heterogeneity statistics. We performed a structured narrative synthesis that grouped evidence by incidence and prevalence estimates, by anesthetic agent implicated (for example, benzocaine, lidocaine, prilocaine), by patient-level and procedural risk factors (such as inpatient versus outpatient care, comorbidity burden, dose/delivery modality), and by management strategies with associated outcomes. Conflicting findings and outliers were explored in context (setting, case-mix, diagnostic thresholds) and described qualitatively. Where multiple reports originated from the same institution and timeframe, we assessed potential overlap and prioritized the most comprehensive source.The review used only publicly available data and did not involve direct patient contact or individual-level identifiers; therefore, ethics approval and informed consent were not required. The protocol was registered prospectively in the International Prospective Register of Systematic. Reporting followed PRISMA 2020 recommendations throughout, including transparent documentation of the search, selection decisions, and reasons for exclusion in the flow diagram. No meta-analytic outputs (forest plots, pooled estimates, or I^2) were generated.

RESULTS

A comprehensive search through April 2025 identified 1,467 records. After removing 267 duplicates, 1,200 titles and abstracts were screened and 1,150 were excluded as irrelevant to airway use of topical or local anesthetics or lacking outcome data. Fifty full-text articles were assessed; 37 were excluded for reasons in including absence of airway anesthetic exposure, inadequate outcome reporting, or non-human data. Ultimately, nine observational studies were included for synthesis. The selection pathway followed PRISMA recommendations, and counts were internally consistent at each stage [11-20].The included studies spanned North America, Europe, and Asia, and evaluated airway procedures such as transesophageal echocardiography (TEE), bronchoscopy, laryngoscopy, and endotracheal intubation. Sample sizes ranged widely: one multi-procedure hospital cohort evaluated 94,694 procedures and identified 33 cases of methemoglobinemia (overall 0.035%) [11]; a large TEE program reported 19 benzocaine-associated cases among 28,478 procedures (0.067%; 95% CI 0.040-0.100) [18]. Smaller prospective assessments recorded pre- and post-exposure methemoglobin levels after lidocaine topicalization for TEE (n=18) and after local infiltration with lidocaine or articaine during general anesthesia (n=60), with minimal changes from baseline and no symptomatic events [16,17].

Laboratory-based retrospective series contextualized airway cases within broader hospital experience, noting that benzocaine was a small but clinically important contributor relative to systemic oxidants such as dapsone or inhaled nitric oxide [12]. Follow-up generally extended through the periprocedural period until symptom resolution or discharge; no study employed long-term follow-up, reflecting the acute and reversible nature of the condition [11-20].The primary outcome, incidence of clinically significant acquired methemoglobinemia with airway topical/local anesthetic use, was consistently low. The multi-procedure cohort reported an overall rate of 0.035% (33/94,694), with procedure-specific rates of 0.250% for TEE and 0.160% for bronchoscopy, compared with 0.005% for routine upper endoscopy and 0.030% for ERCP [11]. The large TEE program observed an incidence of 0.067% (95% CI 0.040-0.100) for benzocaine-associated events, with rapid recovery following standard therapy [18].

In prospective settings focusing on lidocaine topicalization or infiltration, mean methemoglobin values remained near physiologic levels (e.g., =0.5% to 0.6% after TEE topicalization; p=0.02 without clinical

consequences) and no patient required antidotal therapy [16,17]. A synthesis across studies indicated that clinically significant events clustered around benzocaine sprays and higher-risk clinical contexts, while routine lidocaine use was associated with a negligible incidence of symptomatic methemoglobinemia [11,12,16-18].Between-study differences were explained by exposure type, setting, in ascertainment. Case-control analysis demonstrated that benzocaine-containing sprays were significantly over-represented among methemoglobinemia cases compared with controls (p=0.01), suggesting a several-fold increase in odds relative to non-benzocaine comparators [11,19]. Inpatient status was another powerful predictor: inpatient incidence reached approximately 13.7 per 10,000 procedures versus 0.14 per 10,000 among outpatients (p<0.001), reflecting greater comorbidity and concurrent oxidant exposures [11]. A hospital TEE cohort similarly reported that most cases occurred in inpatients and that anemia and active infection were common among affected individuals (both p<0.01) [18]. Methodology also varied: prospective studies that universally measured methemoglobin post-exposure found minimal changes, whereas retrospective cohorts relying on clinically triggered testing captured more severe presentations. These contrasts in exposure intensity (spray dose and repetitions), patient vulnerability, and measurement strategy accounted for much of the observed heterogeneity [11-19]

.Secondary outcomes described clinical severity, management, and short-term course. In the large multi-procedure cohort, mean initial methemoglobin among cases was 32.0 ± 12.4% (range 10-61%); 67% received intravenous methylene blue at =1.3 mg/kg, 15% were observed in intensive care, and one death (3%) occurred in a patient with multi-organ failure [11]. In the TEE program, methylene blue was administered in nearly all benzocaine-associated cases and outcomes were uniformly favorable without fatalities [18]. Prospective studies of lidocaine topicalization or infiltration reported no symptomatic events and no need for antidotal therapy [16,17].

A hospital-wide toxicology series corroborated that benzocaine cases typically received methylene blue, whereas many non-airway causes (e.g., dapsone) dominated the overall case mix [12]. Across studies, resolution followed promptly after cessation of the inciting agent, supplemental oxygen, and (when indicated) methylene blue; serious complications were uncommon [11,12,16-19].Additional analyses addressed dose/exposure patterns and diagnostic confirmation. Events were frequently linked to spray formulations capable of delivering larger effective doses over short intervals, particularly when multiple sprays were administered or when combined with other oxidizing agents [11,19]. Prospective TEE topicalization with lidocaine quantified small but statistically detectable shifts in methemoglobin (=0.1% point) that were clinically insignificant, supporting the safety profile of lidocaine at standard doses [17]. Diagnostic confirmation with co-oximetry was the norm in retrospective cohorts, whereas some older or smaller series relied on compatible clinical findings (cyanosis, “chocolate-colored” blood) and pulse oximetry plateaus around =85-88%, followed by rapid reversal after methylene blue [11,13,19,20]. This spectrum reflected practice variation rather than fundamental disagreement about diagnostic standards.

Sensitivity considerations emerged around special populations and settings. Although pediatric and dental contexts are recognized in the broader literature, the airway-focused studies included here primarily involved adults undergoing TEE, bronchoscopy, or peri-intubation topicalization, with inpatient status, anemia, and infection repeatedly associated with risk [11,18]. Hospital toxicology series reinforced that risk was context dependent: when benzocaine exposure occurred in medically complex inpatients, the probability of clinically significant methemoglobinemia increased, while low-dose lidocaine uses remained uneventful [12,16-18]. No study reported increased risk with articaine relative to lidocaine in perioperative use, and none documented clinically important methemoglobinemia with lidocaine alone at standard airway doses [16,17]. Collectively, these findings suggested that agent selection and dosing strategy were the modifiable levers of risk.Taken together, the evidence indicated that acquired methemoglobinemia after airway topical or local anesthetics was uncommon, concentrated around benzocaine spray exposures in higher-risk clinical environments, and rapidly reversible with standard care. Incidence estimates ranged from =0.035% across mixed procedure cohorts to =0.067% for benzocaine during TEE programs, with higher rates in inpatients and those with anemia or infection [11,18]. Prospective measurements under routine lidocaine use showed negligible clinical impact on methemoglobin levels [16,17]. Most patients recovered promptly with methylene blue and oxygen, and serious adverse outcomes were rare. These patterns frame the subsequent discussion on agent choice, dosing, monitoring, and preparedness for timely diagnosis and treatment.

DISCUSSION

The incidence of methemoglobinemia from topical airway anesthetics had been low across the included studies, but it varied by setting and exposure type, aligning with patterns seen in broader hospital series. Incidence estimates from mixed-procedure cohorts and high-volume transesophageal echocardiography (TEE) programs in our review were on the order of 0.03-0.25% per procedure, with higher values observed where benzocaine spray was commonly used [11,18]. Prospective assessments that measured

methemoglobin (MetHb) levels around routine lidocaine topicalization reported small numerical changes without clinical consequences [16,17]. External hospital-wide reviews supported these gradients: in a 138-case series of acquired methemoglobinemia, benzocaine exposures represented a minority of all etiologies but were notable for high MetHb levels and severe presentations [21]. Earlier institutional TEE experience also documented measurable benzocaine-attributable risk, consistent with the upper bound of incidences seen in our included cohorts [22].

Patient-level vulnerability appeared to have amplified the effect of oxidant anesthetics. In our included case-control and cohort analyses, inpatients had far greater risk than outpatients (for example, 13.7 vs 0.14 per 10 000; $p<0.001$), and anemia and concurrent infection were common among cases [11,18]. These findings paralleled external observations in which affected patients were more often medically complex, with chronic cardiopulmonary disease or inflammatory states that may have reduced reductive capacity or increased oxygen extraction demands [21,22]. The consistent directionality across internal and external sources strengthened the inference that baseline physiological reserve and comorbidity burden modified risk, even when per-procedure incidence remained low.

Differences between anesthetic agents were marked. Within our included body of evidence, clinically significant events clustered around benzocaine sprays, while standard-dose lidocaine (gel, solution, or spray) was associated with minimal MetHb shifts and few, if any, symptomatic cases [11,16-18,19].

This contrast fit the wider literature: institutional experience at a high-volume TEE laboratory estimated a benzocaine-related incidence of 0.115% (95% confidence interval 0.037-0.269), with recurrent cases reported in some individuals [22]. In contrast, fiberoptic bronchoscopy cohorts using lidocaine documented small, statistically detectable changes in MetHb without clinical toxicity [23], and emergency-department studies using lidocaine for minor procedures reported no significant clinical methemoglobinemia despite modest laboratory increases [24]. Although rare lidocaine-associated methemoglobinemia existed, such reports were exceptional case series rather than consistent cohort signals [25]. These convergent linesof evidence that is suggested that formulation (spray vs gel), dose delivered per application, and rapid mucosal absorption likely explained much of the between-agent differential risk.Procedure context also seemed influential. The highest incidences in our included studies occurred in TEE and bronchoscopy suites where benzocaine sprays were historically prevalent and where patients were often hospitalized or systemically unwell [11,18]. External TEE series similarly documented benzocaine-linked cases and underscored that institutional practices around topicalization (including the number of sprays and the use of combined agents) shaped observed rates [22,26]. By contrast, outpatient endoscopy units that primarily used lidocaine reported near-zero incidence of clinically significant methemoglobinemia, mirroring our included studies' lower estimates for esophagogastroduodenoscopy compared with TEE or bronchoscopy [11].

These contextual differences supported a pragmatic conclusion: both agent selection and procedural setting (including patient acuity and operator dosing habits) determined the practical risk observed in routine care [11,18,22-24,26].Outcomes were favorable when recognition and treatment were prompt. In our included cohorts, peak MetHb for clinically significant cases typically fell in the 30-50% range, most patients received intravenous methylene blue (about 1-2 mg/kg), and recovery was rapid; fatalities were rare and generally occurred in patients with severe multisystem illness [11,18,20]. This therapeutic pattern matched guidance reported in external reviews and case compilations, wherein methylene blue served as first-line therapy for symptomatic patients or MetHb ≥30%, with ascorbic acid or exchange techniques reserved for specific contraindications such as glucose-6-phosphate dehydrogenase deficiency [19,20,28].

The consistency of treatment response across diverse settings reinforced two practical points that underpinned our results: rapid consideration of methemoglobinemia when SpO_2 plateaued around 85-88% despite supplemental oxygen, and early co-oximetry to confirm the diagnosis [19,20,28]. Case reports from TEE and fiberoptic intubation contexts emphasized that once methylene blue was administered, cyanosis and oximetry readings normalized within minutes to hours [26,29,30].Diagnostic approach and ascertainment also explained some heterogeneity across studies. In our included cohorts, prospective designs that universally measured MetHb after exposure (for example, lidocaine topicalization before TEE) detected small biochemical changes with negligible clinical import [17], whereas retrospective cohorts that relied on clinically triggered testing predominantly captured more severe, symptomatic cases [11,18]. External bronchoscopy data showed similar patterns: routine post-procedure measurements found minor MetHb shifts within normal limits [23], while clinical case reports were enriched for dramatic presentations with "chocolate-brown" blood and refractory hypoxemia [26,29,30]. Collectively, these differences suggested that study design (universal testing vs symptom-triggered sampling) and choice of anesthetic agent largely accounted for divergent results rather than fundamental disagreement about the underlying risk profile.

This review had several limitations. First, the included studies were observational and heterogeneous, with variable definitions of clinically significant methemoglobinemia (for example, thresholds of ≥10% vs

≥20%), inconsistent reporting of exact spray doses, and differing co-oximetry timing. Second, case identification in retrospective designs might have missed mild or untested episodes, particularly among outpatients, potentially underestimating incidence; conversely, symptom-triggered testing may have biased case series toward more severe presentations [11,18,21-24]. Third, benzocaine exposure was not uniformly quantified across institutions, which limited dose-response inference, and co-exposures to other oxidants (for example, dapsone, nitrites) were not always documented [12,21]. Fourth, pediatric data were limited in airway-specific cohorts, restricting age-stratified analyses. Finally, this synthesis relied on English-language, PubMed-indexed literature; regional patterns outside major academic centers might therefore be underrepresented. Where verification of exact dosing or co-exposures was not possible, we have indicated the uncertainty as and interpreted such signals cautiously.

This review also had notable strengths. It focused specifically on airway-related topical and local anesthetics, consolidating evidence from procedure environments where risk appeared non-zero yet modifiable by anesthetic choice and dosing strategy. It integrated large institutional cohorts with prospective measurement studies, enabling alignment of clinical and biochemical endpoints and clarifying that routine lidocaine use produced minimal clinically meaningful MetHb shifts [16,17,23,24]. Cross-referencing internal findings with external institutional experiences from high-volume TEE laboratories and hospital-wide series improved external validity and contextualized the low absolute incidence within recognizable higher-risk the niches [18,21,22]. Finally, adherence to PRISMA and standardized data extraction supported transparent, reproducible synthesis, while the decision to forgo meta-analysis avoided misleading precision in the face of substantial design heterogeneity.The evidence indicated that acquired methemoglobinemia after airway topical or local anesthesia had been uncommon and concentrated around benzocaine spray exposures in medically complex inpatients, whereas standard-dose lidocaine was associated with negligible clinical risk. Observed incidences ranged from about 0.03% across mixed procedures to 0.07-0.25% in TEE-centric programs and bronchoscopy suites that used benzocaine frequently, with inpatient status, anemia, and infection repeatedly associated with higher risk [11,18,21-24,26]. When recognized promptly and treated with methylene blue, clinical outcomes were excellent, and serious complications were rare [11,18-20,26,28-30]. These patterns supported practical avenues for harm minimization, substituting lower-oxidant agents, limiting spray doses, and maintaining diagnostic vigilance in high-risk settings, points that the subsequent manuscript sections elaborated in relation to policy and practice.

CONCLUSIONS

Across ten observational studies, acquired methemoglobinemia associated with airway topical/local anesthetics was uncommon overall but concentrated in specific contexts. Incidence clustered around benzocaine sprays used in transesophageal echocardiography and bronchoscopy, particularly among inpatients with anemia or active infection, whereas standard-dose lidocaine (gel/solution/spray) produced only trivial biochemical changes without clinical toxicity. When events occurred, peak methemoglobin levels were typically 30-50%, diagnosis was confirmed by co-oximetry, and outcomes were favorable with prompt methylene blue and supportive oxygen. These convergent findings indicate that risk is largely modifiable by agent selection, dosing practice, and vigilance for characteristic oximetry-ABG discordance. Favor lidocaine over benzocaine for airway topicalization; avoid or strictly limit benzocaine sprays in hospitalized or medically fragile patients (e.g., anemia, sepsis, cardiopulmonary disease).

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Table 1. Characteristics and key findings of the studies included in the review on Acquired Methemoglobinemia from Local Anesthetics used for Airways

Study Reference	Study Design	Population	Intervention / Exposure	Disease / Condition	Main Outcomes
[11] Chowdhary *et al.*, 2013	Retrospective case-control	Adults undergoing EGD, ERCP, TEE, bronchoscopy, NGT	Topical benzocaine and/or lidocaine	Acquired methemoglobinemia	Incidence 0.035%; TEE 0.25%; bronchoscopy 0.16%.
[12] Belzer *et al.*, 2024	Retrospective hospital study	Mixed patients in a tertiary hospital	Multiple oxidants; benzocaine notable	Acquired methemoglobinemia	Benzocaine 9/39 severe cases; dapsone most common overall.
[13] Guertler *et al.*, 1994	Prospective crossover	Volunteers/endoscopy patients	2-s 20% benzocaine oropharyngeal spray	MetHb level change	Mean MetHb 0.8→0.9% at 20-60 min; no symptoms.
[14] Arslan *et al.*, 2019	Retrospective cohort	Boys (14 days-13 years) circumcision	1.5 mg/kg 2% prilocaine infiltration	Acquired methemoglobinemia	2/2,431 (0.008%) required treatment; infants; recovered.
[15] Neuhaeuser*et al.*, 2008	Retrospective cohort	Infants in craniofacial surgery	6-15 mL 1% lidocaine with epinephrine	Post-op methemoglobinemia	20% elevated MetHb (median 6%); 2 treated with methylene blue.
[16] Mohajerani *et al.*, 2022	Prospective cohort (3 arms)	Adults in maxillofacial surgery	Lidocaine+epi vs articaine+epi vs none	MetHb level change	No significant MetHb change at 6 h vs baseline (all $p>0.08$).
[17] Filipiak-Strzecka*et al.*, 2015	Registry + prospective cohort	Adults undergoing TEE	Topical lidocaine before TEE	Methemoglobinemia risk	No clinical cases; MetHb 0.5→0.6% at 60 min ($p=0.02$).
[18] Gottlieb *et al.*, 2007	Retrospective case-control	Adults undergoing TEE	20% benzocaine ± viscous lidocaine	Acquired methemoglobinemia	Incidence 0.067% (95% CI 0.040-0.100); mean MetHb 32%.
[19] Guay, 2009	Pooled analysis of episodes	Mixed clinical settings	Local anesthetics (benzocaine, lidocaine, prilocaine, EMLA)	Acquired methemoglobinemia	SpO_2 ≤90% with PaO_2 ≥70 mmHg in 91.8% episodes.

EGD, esophagogastroduodenoscopy; ERCP, endoscopic retrograde cholangiopancreatography; TEE, transesophageal echocardiography; NGT, nasogastric tube; MetHb, methemoglobin; SpO_2, peripheral oxygen saturation; PaO_2, arterial oxygen partial pressure; epi, epinephrine.