Proposed characterization of the syndrome of epidural pneumatosis (pneumorrhachis) in patients with forceful vomiting from diabetic ketoacidosis as a clinico-radiologic pentad based on systematic literature review & an illustrative case report

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Abstract
Background: Previous literature on epidural pneumatosis (pneumorrhachis, or air in epidural cavity) associated with forceful vomiting in a patient with diabetic ketoacidosis (DKA) has consisted of individual case reports without comprehensive syndrome characterization due to syndromic rarity, with the largest previous literature review comprising 6 cases. Presumed pathophysiology is air escaping from alveolar rupture from forceful vomiting via tissue planes to cause epidural pneumatosis.

Aim: Systematically review literature to facilitate syndromic diagnosis, evaluation, and treatment. A new illustrative case is reported.

Methods: Systematic review of literature using 2 independent readers, 2 computerized databases, and the following medical terms/keywords: [epidural pneumatosis] OR [pneumorrhachis] AND [diabetes] OR [diabetic ketoacidosis] OR [DKA]. Discrepancies between 2 readers were resolved by consensus using prospectively developed study inclusion criteria. Two readers independently abstracted case report. Prospective review protocol and patients, problems, intervene, comparison group, outcomes discussed in Methods section of paper.

Results-systematic-literature-review: Revealed 10 previously reported cases plus 1 new case (see below) that shows this syndrome presents rather stereotypically with the tentatively proposed following pentad (% of patients fulfilling individual criterion): 1-forceful vomiting (100%), 2-during DKA (100%), 3-pneumomediastinum from forceful alveolar rupture (100%), 4-epidural pneumatosis from air escape from pneumomediastinum (100%), and 5-no complications of Boerhaave syndrome or of focal neurological deficits (100%). Pentad is pathophysiologically reasonable because forceful vomiting can cause alveolar rupture, pneumomediastinum, and air entry into epidural space.

Results-illustrative-case-report: Epidural pneumatosis occurred in a 33-year-old-male with poorly controlled diabetes mellitus type 1 who presented with forceful vomiting while in DKA. Radiologic findings also included subcutaneous emphysema.

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pneumomediastinum, and small pneumothorax. The patient rapidly improved while receiving acute therapy for DKA, and was discharged after 2 hospital days.

**Study limitations:** Limited number of analyzed, retrospectively reported cases. Case reports subject to reporting bias. Specificity, positive predictive value, and negative predictive value not meaningfully analyzed in this homogeneous population.

**Conclusions:** Based on systematic review, syndrome is tentatively proposed as a pentad with: 1-forceful vomiting, 2-during DKA, 3-pneumomediastinum, 4-epidural pneumatosis, and 5-no complications of Boerhaave syndrome or focal neurological deficits. Proposed pentad should be prospectively tested in a larger population including patients with this versus closely related syndromes.

**Abbreviations:** BUN = blood urea nitrogen, CT = computerized tomography, IV = intravenous.

**Keywords:** Boerhaave syndrome, diabetic ketoacidosis, epidural pneumomediastinum, pneumorrhachis, vomiting

1. **Introduction**

Epidural pneumatosis (pneumorrhachis or air in epidural cavity) is a rare radiologic entity often secondary to epidural trauma from spinal fracture, epidural injection usually for epidural anesthesia, and epidural instrumentation for lumbar puncture,[12] or apparently “spontaneous” pneumomediastinum.[13] Another rare cause is forceful vomiting in patients with diabetic ketoacidosis (DKA) which presumably causes pulmonary alveoli to rupture and alveolar air to escape and dissect through tissue planes to produce pneumomediastinum and epidural pneumatosis. This systematic literature review identifies 10 previously reported cases of this syndrome,[3–12] expanding the largest previous review of 6 cases[3]; reports a new, eleventh (illustrative) case; and tentatively characterizes this syndrome as a novel pentad that facilitates syndrome evaluation, diagnosis, and therapy.

2. **Methods**

Systematic literature review used 2 computerized databases of PubMed & Medline with last search performed on January 20, 2020, 2 independent reviewers/authors, and the following medical terms/keywords: [“epidural pneumatosis” OR “pneumorrhachis”] AND [“diabetes” OR “diabetic ketoacidosis” OR “DKA”]. Cases were included in this systematic review by consensus to resolve discrepancies, according to the following prospective criteria: confirmed diabetes mellitus (DM); antecedent vomiting; DKA conclusively diagnosed by standard laboratory criteria; and radiologic diagnosis of epidural pneumatosis. Review included all types of publications beginning in 2001 (earlier publications omitted due to inferior computerized tomography [CT] quality). The systematic review followed the PRISMA guidelines,[13] and used the PRISMA Flow Diagram to show filtering of articles for this systematic review (Fig. 1). All clinical parameters (eg, symptoms, signs, laboratory values) for every reported patient were independently abstracted by 2 readers to minimize errors. Statistical analyses were performed independently by 2 analysts to minimize errors. “Patients, problems, intervene, comparison group, outcomes” parameters[14,13] included: Patients—all patients, male or female, and of any age or race except for patients with abnormal esophageal anatomy from major esophageal surgery or congenital anomalies which could anatomically interfere with the vomiting causing epidural pneumomediastinum; Problem–forceful vomiting during DKA causing epidural pneumatosis from escape of air from pulmonary alveoli via pneumomediastinum; Intervene—diagnose syndrome and aggressively treat DKA; treatment of epidural pneumatosis unnecessary in absence of neurologic symptoms of cord compression; Comparison group–failure to implement prompt specific therapy for DKA (no failures occurred); and Outcomes—morbidity or mortality from DKA, missed esophageal rupture, or undiagnosed spinal cord compression.

Prospective review protocol per patient per analyzed publication included: (history & symptoms) presence, type, and duration of DM; presence of vomiting; type of vomiting, whether forceful, severe, or recurrent; other symptoms including neck pain, dyspnea, pyrexia, epigastric pain, pyrosis, confusion & headache, and other; (signs) including tachycardia, signs of dehydration (dry mucous membranes, absent axillary sweat, poor skin turgor, or orthostasis), tachypnea, hypertension, Kussmaul breathing, subcutaneous crepitations, Hamman sign (defined as a crunching and rasping sound, synchronous with the pulse, heard by auscultation over the precordium in mediastinal emphysema, attributed to the heart beating against air-filled mediastinal tissue), epigastric tenderness, focal neurologic deficits, and other; (metabolic abnormalities characteristic of DKA on admission) including highly elevated serum glucose, acidic pH on arterial blood gas, decreased serum bicarbonate level due to metabolic acidosis, ketone bodies in blood and urine, and high anion gap acidosis; (other laboratory abnormalities) including elevated blood urea nitrogen (BUN), elevated serum creatinine, leukocytosis, and polycythemia from hemoconcentration; (radiologic findings of abnormal air collections on chest radiographs and chest CT) including epidural pneumatosis, pneumomediastinum, subcutaneous emphysema, pneumothorax, pneumopericardium, and pneumoretroperitoneum; (barium or gastrografin esophageal swallow findings) of no esophageal leak/rupture; (patient treatment) including intravenous (IV) insulin, IV fluid, IV sodium bicarbonate, IV potassium, and supplemental oxygen; and (patient outcome) including intensive care unit admission, length of hospital stay, resolution of DKA, resolution of radiologic abnormalities before discharge, patient morbidity, and mortality.

The case report received exemption/approval from the Institutional Review Board of Beaumont Hospital at Royal Oak on December 16, 2019. The case report followed the CARE guidelines. All authors took full responsibility for anonymization of patient data. The patient agreed to publication of the anonymized case report as submitted. To prevent errors, 2 authors independently abstracted the case report from the electronic medical record, and resolved discrepancies by consensus. Radiologic films were professionally re-reviewed.

3. **Systematic review**

Systematic literature review revealed 10 previously reported patients (Table 1), to which is added a newly reported patient (see
All 11 patients had (severe, forceful, or recurrent) vomiting. All patients had DM: history of DM type 1 in 6 patients (3, 4, 6, 10, 12, current report), DM of unspecified type-3,[7,8,11] and DM newly diagnosed on admission-2.[5,9] All patients had metabolic abnormalities “characteristic of DKA,” including 4 case reports not listing their initial laboratory values,[4,8,10,11] and 7 patients with listing of the following metabolic abnormalities that were highly characteristic of DKA (3, 5, 6, 7, 9, 12, current report): mean glucose level = 633 ± 152 (SD) mg/dL (range: 426–823 mg/dL, median = 667 mg/dL, N = 7); severely acidic pH on arterial blood gas-5[3,5,7,9,12]; decreased serum sodium bicarbonate level due to metabolic acidosis-5[3,5,6,7,12] or borderline low serum bicarbonate-1 (current report); excessive ketone bodies in blood-4[3,5,7,9] or in urine-4[5,6,9,12]; high anion gap acidosis-2[7,9] or severe base deficit-2[6,12]; and elevated beta hydroxybutyrate-1 (current report).

All patients (100%), had epidural pneumatosis, as uniformly diagnosed by chest CT. Pneumomediastinum was diagnosed by chest radiographs, performed in 10 patients (not performed in 1–11) (100%; 3, 4, 5, 6, 7, 8, 9, 10, 12, current report), and was diagnosed by chest CT, performed in all 11 patients (100%; 3–12, current report). The 10 chest radiographs also revealed subcutaneous emphysema-8 (80%; 4, 6–10, 12, current report); pneumothorax-1 (10%; 5), and pneumopericardium-1 (10%; 6). Subcutaneous emphysema was localized to the lower neck and/or upper chest wall. The 11 chest CTs also revealed subcutaneous emphysema-7 (4, 5, 7, 10, 11, 12, current report); pneumothorax-3 (6, 8, current report); pneumopericardium-1[10]; and pneumoretroperitoneum-1.[11] Signs of air in subcutaneous planes or in other cavities included subcutaneous crepitations-6 (3, 4, 8, 11, 12, current report), or Hamman sign-5.[4,5,6,7,12] Symptoms included chest pain-5 (4, 7, 8, 10, current report); neck pain-3[13,10,12]; dyspnea-3 (4, 9, current report); pyrexia-3[7,8,11]; and 1 each with epigastric pain, pyrosis,[6] and confusion & headache.[9] Other signs included tachycardia-7 (3, 6, 7, 8, 9, 12, current report); signs of dehydration of dry
Clinical presentation in 11 reported cases of epidural pneumatosis associated with vomiting in diabetic ketoacidosis.

| Case reports                        | Laboratory values | Radiologic and endoscopic findings | Clinical course | Reference (type of publication) |
|-------------------------------------|-------------------|------------------------------------|-----------------|---------------------------------|
| 33 y. o. M with poorly controlled DM type 1 presented with forceful vomiting followed suddenly by chest pain and dyspnea. PE: HR = 118 beats/min, BP = 131/85 mm Hg, RR = 18 breaths/min. Dry mucus membranes, absent axillary sweat, poor skin turgor. Subcutaneous crepitance over upper chest wall and lower neck. | WBC = 14,000/mm³, Hgb = 17.3 gm/dL, BUN = 17 mg/dL, creatinine = 1.76 mg/dL, glucose = 426 mg/dL, sodium bicarbonate = 20 mmol/L, beta hydroxy-butyrate = 2.4 mmol/L. | Chest radiograph: pneumomediastinum and subcutaneous emphysema in anterior neck and chest wall. | Treated for DKA with IV fluids, IV insulin, and IV potassium. Repeat chest radiograph showed improved subcutaneous emphysema. Discharged on day 2. | CURRENT REPORT |
| 20 y. o. F with DM presented with recurrent vomiting, pleuritic left-sided chest pain, and fever. PE: HR = 106 bpm, BP = 150/78 mm Hg, orthostasis present, RR = 20/min, subcutaneous crepitations on left neck and Hamman crunch sign. | Initial glucose = 671 mg/dL, Hgb = 16.7 gm/dL, pH = 7.17, bicarbonate = 16 meq/L, anion gap = 24, elevated serum ketones, BUN = 31 mg/dL, creatinine = 2 mg/dL. | Chest radiograph: Mediastinal air along left heart border and along left neck. No pneumothorax. Chest CT: Air in soft tissues of neck, pneumomediastinum, epidural pneumatosis along prevertebral area of thoracic spine. | Treated for DKA. All the pneumomediastinum resolved radiologically. Discharged home in good condition. | Paoysan P., et al, 2004[7] |

(continued)
Table 1

(continued).

| Clinical presentation | Laboratory values | Radiologic and endoscopic findings | Clinical course | Reference (type of publication) |
|-----------------------|-------------------|-----------------------------------|----------------|---------------------------------|
| Single case described briefly in a table or in a clinical series | | Gastrografin swallow: no esophageal leak/ perforation. | | |
| 30 y. o. M presenting with chest pain and neck swelling after 3 d of vomiting. History of poorly controlled DM. PE: pyrexia, tachycardia, subcutaneous crepitus. | | Chest radiograph: pneumomediastinum, subcutaneous emphysema. Chest CT: pneumomediastinum, bilateral pneumothorax, epidural emphysema, and pneumoretroperitoneum. Contrast swallow: no esophageal perforation/leak. | Treatment for DKA including insulin, fluid and electrolyte resuscitation. Discharged after 5 d in hospital. | Forshaw MJ et al, 2007 (case #4 in a clinical series)[9] |
| 18 y. o. M presented with vomiting, confusion, and dyspnea after administration of high dose oral prednisone for rash of neck and chest. PE: altered mental status, tachycardia, and Kussmaul respirations. Patient not previously known to be diabetic. | WBC = 24.8/mm³, bicarbonate = 5 mmol/L, pCO₂ = 24.8 mmHg, pH of venous blood = 6.90, pCO₂ = 21 mm Hg. | Chest radiograph: subcutaneous emphysema, pneumomediastinum. Chest CT: epidural pneumatisosis, epidural emphysema. Barium swallow not performed because no suspicion of esophageal injury. | Treated for DKA with IV fluids and insulin. Initially required endotracheal intubation and mechanical ventilation. Prompt DKA therapy resulted in rapid extubation and resolution of radiographic abnormalities. | Desa PP, et al, (Abstract)[10] |
| 23 y. o. M with DM type 1 presenting with vomiting and sharp pain of neck and chest wall | | Chest radiograph: pneumomediastinum, pneumoretroperitoneum, cervical and thoracic emphysema, and epidural pneumatisosis. | Patient fully recovered from treatment with DKA with regression of radiologic findings of pneumatisosis. | Hall WB, et al, 2012 (clinical image)[11] |
| 19 y. o. M with history of DM and bronchial asthma presented with cough, fever, nausea, and vomiting for 4 d. PE: cervical crepitus. | Hyperglycemia and other laboratory tests “demonstrating DKA.” | Chest CT: pneumomediastinum, pneumoretroperitoneum, cervical and thoracic emphysema, and epidural pneumatisosis | Underwent otolaryngologic exploration which revealed no abscess. Received standard therapy for DKA, IV antibiotic therapy, and anti-nausea medications. Epidural pneumatisosis resolved completely and discharged after 12 d feeling well. | Oertel MP, et al, 2004 (neurology picture)[12] |
| 23 y. o. M with DM type 1 presented with persistent vomiting and anorexia for 1 d, and epigastric and neck pain. PE: HR = 127 bpm, BP = 134/76 mm Hg; RR = 24 breaths/min, venous O₂ saturation = 100% on RA. Dry mucous membranes. Subcutaneous crepitations over lung apices and lateral neck, Hamman crunch sign, mild epigastric tenderness. | Initial blood glucose = 42.2 mmol/L, positive urine ketones, Hgb = 17.3 g/dL, WBC = 44.5 × 10⁹/L, BUN = 31.1 mg/dL, creatinine = 158 micromol/L, bicarbonate = 9 mmol/L, ABG pH = 7.17, pCO₂ = 27 kPa, base excess = −18.5. | Chest radiograph: subcutaneous emphysema, pneumomediastinum. Chest CT: air in soft tissues, pneumomediastinum, epidural pneumatisosis. Gastrografin swallow: no esophageal perforation/leak. | “Standard treatment for DKA” and administration of supplemental oxygen. Did well and discharged. | Ripley DP, et al, 2009 (letter)[13] |

**ABB** = arterial blood gas, **BP** = blood pressure, **BUN** = blood urea nitrogen, **CT** = computerized tomography, **DKA** = diabetic ketoacidosis, **ESG** = esophagogastroduodenoscopy, **F** = female, **Hgb** = hemoglobin, **HR** = heart rate, **IV** = intravenous, **M** = male, **PE** = physical exam, **RA** = room air, **RR** = respiratory rate, **WBC** = white blood cell (count), y. o. = years old.
mucous membranes, absent axillary sweat, poor skin turgor, and/or orthostasis-4 (4, 7, 12, current report); tachypnea-4 (≥ 20 breaths/min; 3, 6, 7, 12); hypertension-3 (6, 7, current report); Kussmaul breathing-2 [3, 9]; and epigastric tenderness-2 [6, 12].

Other laboratory abnormalities included elevated BUN-5, [3, 6, 7, 9, 12] and creatinine-4 (3, 7, 12, current report), which most likely arose from hypovolemia due to polyuria or acute kidney injury from DKA. Four patients had leukocytosis (3, 9, 12, current report), most likely from physiologic stress or infection associated with DKA. Two patients had polycythemia (Hgb > 17.0 mg/dL; 12, current report), and 2 others had borderline polycythemia (Hgb > 16.5 mg/dL; 3, 7), most likely from hemoconcentration from hypovolemia with DKA.

Exclusion of Boerhaave syndrome is important because vomiting sufficiently forceful to produce pneumomediastinum and epidural pneumatoasis might cause esophageal rupture, which is life-threatening if not diagnosed and treated quickly. [14, 15] Eight patients had no esophageal leak/perforation as confirmed by barium swallow-4 (3, 4, 10, current report), gastrografin swallow-2, [7, 12] or swallow using an unspecified contrast agent-2. [6, 8] Oral contrast swallow was not performed in 3, [5, 9, 11] but their benign subsequent clinical course was inconsistent with Boerhaave syndrome. Excluding focal neurologic deficits is important because patients with such deficits may require laminectomy or other neurosurgery, as reported for patients with epidural pneumatoasis without DKA. [2, 16] No patient had focal neurologic deficits.

Patients typically presented as acutely ill, required initial management in an intensive care unit due to DKA, and recovered rapidly, with rapid resolution of symptoms and reversal of metabolic abnormalities after treatment of DKA with IV insulin, IV fluids, and frequent administration of IV sodium bicarbonate, IV potassium, and supplemental oxygen. While the radiologic phenomenon of pneumatoasis in body cavities including epidural pneumatoasis is typically a relatively benign radiologic phenomenon, the DKA is initially a life-threatening emergency requiring prompt emergency therapy. Radiologic regression of pneumatoasis in body cavities usually took more time than symptomatic relief.

### 4. Case report

A 33-year-old-male with a past medical history of poorly controlled DM type 1, and 1 prior episode of DKA, presented with nausea and multiple episodes of forceful vomiting, suddenly followed by pleuritic chest pain and dyspnea. On admission, vital signs revealed a pulse of 118 beats/min, blood pressure of 131/85 mm Hg, respiratory rate of 18 breaths/min, and O₂ saturation of 97% on room air. Physical examination revealed dry mucous membranes, absent axillary sweat, and poor skin turgor; subcutaneous crepitation over the upper chest and neck; and soft, non-tender, and non-distended abdomen, with normal bowel sounds, and no hepatosplenomegaly. Routine laboratory tests on admission revealed DKA with leukocytosis, hemoconcentration (from dehydration), normal BUN level, elevated creatinine level (from mild acute kidney injury), hyperglycemia,
borderline low sodium bicarbonate level, elevated beta hydroxybutyrate, and normal potassium level (Table 2).

Chest radiographs showed pneumomediastinum, and subcutaneous emphysema in neck and chest wall (Fig. 2A and B). Chest CT with IV contrast revealed epidural pneumatosis, pneumomediastinum, subcutaneous emphysema, and trace right pneumothorax (Fig. 3A–C). Patient received supplemental oxygen at 2L/min via nasal cannula. DKA, diagnosed by the aforementioned laboratory abnormalities, was treated with profuse IV fluid hydration, IV insulin therapy, and potassium at 20meq/L. Barium esophagram revealed no contrast extravasation from the esophagus. Neurosurgical and thoracic surgery consultations recommended conservative management due to absence of neurological deficits and of esophageal leak/rupture, respectively. Repeat chest radiograph on hospital day 2 demonstrated improvement in subcutaneous emphysema, with no change in pneumomediastinum. Patient was discharged home 2 days after admission, with supportive management, and has been asymptomatic during 3 months of follow-up.

5. Discussion

Review of 10 prior cases identified by systematic literature review, plus the currently reported case, showed that this syndrome presents stereotypically. This syndrome is tentatively proposed as a novel clinico-radiologic pentad of:

1. (severe, forceful or recurrent) vomiting (reported in 100%);
2. in a diabetic patient with a constellation of metabolic abnormalities characteristic of DKA (reported in 100%);
3. pneumomediastinum from forceful vomiting (shown by chest radiograph or chest CT in 100% of cases);
4. epidural pneumatosis (in 100% of cases), as demonstrated by chest CT; and
5. no complications of esophageal rupture (Boerhaave syndrome) as demonstrated by barium/gastrografin swallow, and no focal neurologic deficits, as determined by formal neurological/neurosurgical examination (in 100%).

Epidural pneumatosis rarely presents with neurological deficits and resolves on its own with conservative therapy in 98% of cases due to air resorption via the bloodstream. Life-threatening infection should be excluded as precipitating the DKA.

This proposed pentad is pathophysiologically reasonable. Diabetic patients frequently experience forceful vomiting (#1) during DKA (#2). This force can cause alveolar rupture and pneumomediastinum (#3), with air penetrating into epidural space via the posterior mediastinum because it lacks fascia separating it from epidural space (#4); #1. Boerhaave syndrome
and focal neurologic deficits, such as radiculopathy, must be excluded because these complications of forceful vomiting may necessitate esophageal surgery or neurosurgery (e.g., laminectomy), respectively.\textsuperscript{16–18} The clinical presentation, work-up, and proposed pentad are illustrated in Figures 4A and B.

Thoracoscopic interventions or posterior peroral endoscopic myotomy for achalasia can cause severe benign pneumomediastinum with submucosal emphysema, but unlike forceful vomiting during DKA, do not produce epidural pneumatoasis. These iatrogenic perforations, unlike forceful vomiting, produce a focal traumatic rent of serosal or enveloping tissue due to extreme direct pressure mediated by an instrument with secondary air leak without propagating a pressure wave, whereas forceful vomiting during DKA produces a forceful pressure wave of air flow that can reach the epidural space.

Clues of Boerhaave syndrome include chemical mediastinitis from leakage of acidic gastric contents,\textsuperscript{8} pleural effusion, or hydropneumothorax.\textsuperscript{8,19} Chest CT scan with oral contrast can identify areas of esophageal inflammation and rupture with moderate sensitivity and specificity.\textsuperscript{8,17,19} but esophageal contrast swallow is much more definitive.\textsuperscript{8,17,20} For contrast swallows, gastrografin (water soluble) contrast may be superior to barium (oil soluble) contrast because barium can cause chemical mediastinitis in case of esophageal rupture.\textsuperscript{10}

6. Study limitations

This systematic review is limited by the relatively small number of reported cases, by all cases consisting of individual, retrospectively reported, case reports, and potential reporting (selection) bias in that dramatic cases are more likely to be reported. Each of the 5 criteria in the pentad has a diagnostic sensitivity of 100\%, but specificity, positive predictive value, and negative predictive value of each criterion could not be meaningfully assessed without studying a larger population containing patients with this and closely related, but different, syndromes. This pentad should be tested in a larger prospective trial including patients with this syndrome versus closely related disorders.

7. Conclusions

Systematic literature review revealed 10 reported cases, plus 1 currently reported illustrative case, of epidural pneumatosis

**Figure 4.** (A) Algorithm showing initial presentation of syndrome, including 4 of the 5 proposed clinical pentad. (B) Algorithm showing therapy for diabetic ketoacidosis, further work-up of patient to excluded Boerhaave syndrome and focal neurologic deficits (pentad criterion #5), and typical clinical course.
associated with forceful vomiting in a patient in DKA. This syndrome is tentatively proposed as a novel pentad including: 1-forceful vomiting, 2-during DKA, 3-causing pneumomediastinum, 4-causing epidural pneumatosis from air leak, and 5-without esophageal rupture or focal neurologic deficits. This pentad has 100% reported sensitivity in the 11 reported cases. This novel pentad may be clinically useful for diagnosis and treatment.

Author contributions
Conceptualization: Inayat Gill, Ahmed Edhi, Mitchell Cappell.
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