

## SUPPLEMENTARY APPENDIX

### Supplementary Table 1: PubMed/Embase Literature Search Strategy

(“1999/01/01”[PDat] : “2019/09/30”[PDat]) AND (Humans[MeSH] OR adult\*[TIAB] OR man[TIAB] OR woman[TIAB] OR child[TIAB] OR neonate[TIAB] OR newborn[TIAB] OR boy[TIAB] OR girl[TIAB] OR patient[TIAB] OR subject[TIAB] OR cases[TIAB] OR “Case Reports”[pt] OR mixups[TIAB]) AND English[lang] AND (((error\*[TIAB] OR erroneous\*[TIAB] OR wrong\*[TIAB] OR accidental[TIAB] OR uninten\*[TIAB] OR inadvertent\*[TIAB] OR “near-miss”[TIAB] OR “near miss”[TIAB] OR “near misses”[TIAB] OR “Medication Errors”[MeSH] OR “drug errors”[TIAB] OR “drug error”[TIAB] OR “wrong route”[TIAB] OR “medication error”[TIAB] OR “medication errors”[TIAB] OR misadministrat\*[TIAB] OR maladminist\*[TIAB] OR unknowingly[TIAB] OR confus\*[TIAB] OR faulty[TIAB] OR mistake\*[TIAB] OR preventable[TIAB] OR avoid\*[TIAB] OR “Inadvertent injection”[TIAB] OR “Inadvertent infusion”[TIAB] OR (inadvertent[TIAB] AND intravenous[TIAB]) OR “Accidental injection”[TIAB] OR “Accidental infusion”[TIAB] OR “incident reporting system”[TIAB] OR mixup[TIAB] OR “mix-up”[TIAB] OR “mix-ups”[TIAB]) AND (ventricular[TIAB] OR extradural[TIAB] OR peridural[TIAB] OR subarachnoid[TIAB] OR caudal[TIAB] OR blockade[TIAB] OR epidural[TIAB] OR intrathecal[TIAB] OR spinal[TIAB] OR peripheral[TIAB] OR “nerve block”[TIAB] OR anaesth\*[TIAB] OR anesth\*[TIAB] OR inject\*[TIAB] OR infus\*[TIAB] OR syringe\*[TIAB] OR “Inadvertent injection”[TIAB] OR “Inadvertent infusion”[TIAB] OR (inadvertent[TIAB] AND intravenous[TIAB]) OR (inadvertent[TIAB] AND injection[TIAB]) OR route\*[TIAB] OR “Drug Administration Routes”[MeSH] OR “mode of delivery”[TIAB]) AND (connector\*[TIAB] OR misconnect\*[TIAB] OR interconnect\*[TIAB] OR tube[TIAB] OR tubing[TIAB] OR “bore”[TIAB] OR “universal connector”[TIAB] OR “connector design”[TIAB] OR “tubing design”[TIAB] OR luer[TIAB] OR “non-luer”[TIAB] OR “universal design”[TIAB] OR (universal[TIAB] AND tubing[TIAB]) ) OR “Drug Labeling”[MeSH] OR “Drug Overdose”[MeSH] OR deadly[TIAB] OR “incident monitoring”[TIAB])) OR (deadly[TIAB] AND mixups[TIAB]) OR “accidental epidural”[TIAB] OR “accidental injection”[TIAB] OR “accidental intravenous injection”[TIAB] OR “caudal epidural”[TIAB] OR (inadvertent[TIAB] AND (epidural[TIAB] OR caudal [TIAB] OR intrathecal[TIAB] OR “i.v.”[TIAB])) OR (accidental[TIAB] AND (intrathecal[TIAB] OR subarachnoid[TIAB])) OR “organisational accidents”[TIAB] OR “anesthetic incidents”[TIAB] OR (“Safety”[MeSH] AND “Injections, Spinal”[MeSH] AND “Injections, Intravenous”[MeSH]) OR “Accidental subarachnoid injection”[TIAB] OR (accidental[TIAB] AND (intrathecal[TIAB] OR caudal[TIAB] OR epidural[TIAB] OR spinal[TIAB])) OR (“Luer lock”[TIAB] AND misconnection[TIAB]))

MeSH, medical subject heading; TIAB, title or abstract.

## Supplementary Table 2: Case Studies of Misconnection Error Leading to Wrong-Route Connection

### **Intrathecal Vincristine Injection in a Child With Acute Lymphocytic Leukemia**

A 2002 case report describes the accidental intrathecal injection of vincristine in a 12-year-old girl under treatment for acute lymphocytic leukemia (ALL), with no history of neurologic deficit. Despite immediate recognition of the error and subsequent aggressive treatment, the patient's condition deteriorated until death from myeloencephalopathy occurred on day 83 following the incident.<sup>71</sup>

On day 1 of the patient's hospital stay, ALL remission was induced using prednisone. On day 2, the following treatment regimen was implemented: intravenous (IV) vincristine and daunoblastine, and intrathecal methotrexate, hydrocortisone, and cytosine arabinoside. During intrathecal administration, 2 mg of vincristine in 20 mL of diluent was also injected. The error was discovered at 30 minutes and treatment was initiated. A lumbar puncture was used to drain 35 mL of cerebrospinal fluid (CSF) and instill 15 mL of lactated Ringer solution, followed by the removal of an additional 15 mL of CSF. The patient was kept sitting upright, then implanted with an Ommaya reservoir and a lumbar subarachnoid catheter.<sup>71</sup>

The patient tolerated the procedures well, and at 3 hours following the original treatment, was given an infusion of lactated Ringer's solution with fresh frozen plasma through the Ommaya reservoir, with simultaneous catheter drainage. She was also given oral glutamic acid and pyridoxine, with no apparent effect.<sup>71</sup>

The patient's neurologic condition then deteriorated, beginning with declining reflex responses, and progressing to confusion, ascending paralysis, respiratory failure, coma, and death on day 83.<sup>71</sup> Chemotherapy was continued with good response until the patient's death, with blood and bone marrow free of blast cells and no evidence of leukemia found on postmortem examination.<sup>71</sup> The only significant postmortem findings were neuropathologic: the brain, brainstem and spinal cord were soft; the spinal cord showed massive necrosis with total destruction of both grey and white matter; and the cerebellar tissue was extensively damaged.<sup>71</sup>

### **Injection of High-dose Gadolinium Into Extraventricular Drain in a Middle-aged Man Undergoing Magnetic Resonance Imaging**

A 2016 report describes the case of a 59-year-old man undergoing magnetic resonance imaging (MRI) with gadolinium contrast following craniotomy. The accidental administration of gadolinium into the patient's extraventricular drain (EVD) tubing led to severe, irreversible neurological damage.<sup>96</sup>

The patient originally underwent 2 uneventful surgeries, 2 days apart, to treat a right tentorial meningioma; this included the placement of an EVD.<sup>96</sup> For the first 2 days post-craniotomy, the patient had normal intracranial pressure, CSF drain output, and computed tomography results.<sup>96</sup> After a routine MRI on day 3, accompanied by the administration of gadolinium 10mL, the patient complained of nausea and became acutely hypertensive. Intracranial pressure readings were 3 to 9 mm Hg, and the patient was alert and oriented, but anxious. His symptoms resolved for the evening with lorazepam and temazepam administration.<sup>96</sup>

The following morning, the patient's status noticeably declined; he developed rapidly progressing aphasia, right facial droop, and delirium. A review of the previous night's MRI and an MRI of the contents of the EVD reservoir bag revealed the presence of intrathecal gadolinium.<sup>96</sup> The patient was voluntarily intubated, and intensive treatment was initiated to reduce cerebral edema, prevent seizures, mitigate damage from a left posterior cerebral artery infarct, and keep him sedated.<sup>96</sup> The next day, the patient's neurologic state deteriorated further. Nonconvulsive status epilepticus was identified via

continuous electroencephalography; this was treated with lorazepam. The patient received IV phenytoin and levetiracetam, and had a lumbar drain placed.<sup>96</sup>

The patient remained comatose with intermittent seizures that were treated with escalated antiepileptic drug doses and adjustments. He received a tracheostomy and gastrostomy and was transferred to a skilled nursing facility after 2 months. At 2 years, the patient was awake but not interactive or communicative with his environment.<sup>96</sup>

Gadolinium diethylenetriamine penta-acetic acid encephalopathy has been documented in other cases where gadolinium was found in the CSF after intrathecal or intravascular administration, with acute neurological symptom development.<sup>96</sup> While not approved by the US Food and Drug Administration, in studies it has been found to be safe for magnetic resonance cisternography and myelography at low levels. In this case, the patient received 50 to 100 times the maximum recommended dose, given under pressure as an IV push.<sup>96</sup> The authors recognize the need to replace the Luer connector system with one that will eliminate the possibility of human error.<sup>96</sup>