Antibody-Drug Conjugates: The Toxicities and Adverse Effects That Emergency Physicians Must Know

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Antibody-drug conjugates are novel antineoplastic agents whose use is expanding, both in terms of the number of drugs and the number of patients being treated. This article reviews the known toxicities and complications of antibody-drug conjugates that are currently approved for the treatment of cancer in the United States, with a focus on their emergency presentation and management. Similar to many other cancer therapies, most antibody-drug conjugates can cause diarrhea, nausea/vomiting, rash, peripheral neuropathy, and cytopenia, which are generally treated following standard-of-care. Interstitial lung disease, which may mimic pneumonia and cause respiratory failure and death, has been seen with trastuzumab deruxtecan and mirvetuximab soravtansine; emergency treatment of this condition includes oxygenation, ventilatory support, and corticosteroids. Inotuzumab ozogamicin and gemtuzumab ozogamicin are both associated with sinusoidal obstruction syndrome, a potentially fatal liver dysfunction that presents with weight gain, fluid overload, and jaundice. Abnormal liver function tests in patients who have been recently treated with these agents should be cautiously evaluated. Cardiac adverse events with antibody-drug conjugates are rare, but trastuzumab emtansine and trastuzumab deruxtecan may cause a decrease in cardiac contractility, and heart rate corrected QT interval prolongation is a rare effect of trastuzumab deruxtecan. Ocular adverse events, especially blurred vision, and keratopathy, are common with mirvetuximab soravtansine and tisotumab vedotin. Progressive multifocal leukoencephalopathy has been reported with brentuximab vedotin and polatuzumab vedotin. Tumor lysis syndrome may occur after treatment with gemtuzumab ozogamicin, polatuzumab vedotin, and brentuximab vedotin. Patients receiving enfortumab vedotin or brentuximab vedotin may develop hyperglycemia, sometimes presenting as diabetic ketoacidosis. Tisotumab vedotin and trastuzumab emtansine are associated with bleeding; although it is minor in most cases, severe bleeding and intracranial hemorrhage have occurred. Several antibody-drug conjugates can cause an anaphylactoid infusion-related reaction, which occurs most commonly during or soon after infusion but may be delayed up to 24 hours. Further research is needed to establish the real-world incidence of rare complications and how often patients with these complications present to the emergency department. [Ann Emerg Med. 2025;85:214-229.]

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INTRODUCTION

The landscape of cancer treatment is constantly evolving, with novel therapies such as antibody-drug conjugates bringing increased life expectancy and new hope for cure but also toxicities and other complications. As antibody-drug conjugate use increases, so does the presentation of antibody-drug conjugate-associated adverse events to emergency departments (EDs). Some of these events are rare, but they are treated most effectively if they are recognized early.

Antibody-drug conjugates are a targeted anticancer treatment composed of 3 parts: antibody, linker, and bioactive payload.[1] Antibody-drug conjugates are designed to perform targeted delivery of potent toxins while minimizing systemic toxicity.[2] A monoclonal antibody that binds to an antigen that is primarily expressed on the surface of cancer cells allows antibody-drug conjugates to target cancer cells (ie, "guidance system"). A covalent linker that is not hydrolysable in plasma keeps the highly cytotoxic drug (ie, "payload") attached to the antibody. Once the antibody-drug conjugate has bound to its target and is endocytosed, the linker is hydrolyzed to release the cytotoxin to exert its cell-killing effect (Figure). Given the antineoplastic efficacy of this approach, many antibody-drug conjugates have been recently approved by the US Food and Drug Administration (Table 1). Currently, the cytotoxic mechanisms of the cytotoxins in the approved antibody-drug conjugates fall into 2 categories: DNA-damaging agents and microtubule inhibitors (Table 2). Antibody-drug conjugates appear to result in reduced or ameliorated side effect profiles compared with nontargeted delivery of classic antineoplastic agents with similar cytotoxic mechanisms (Table 3).

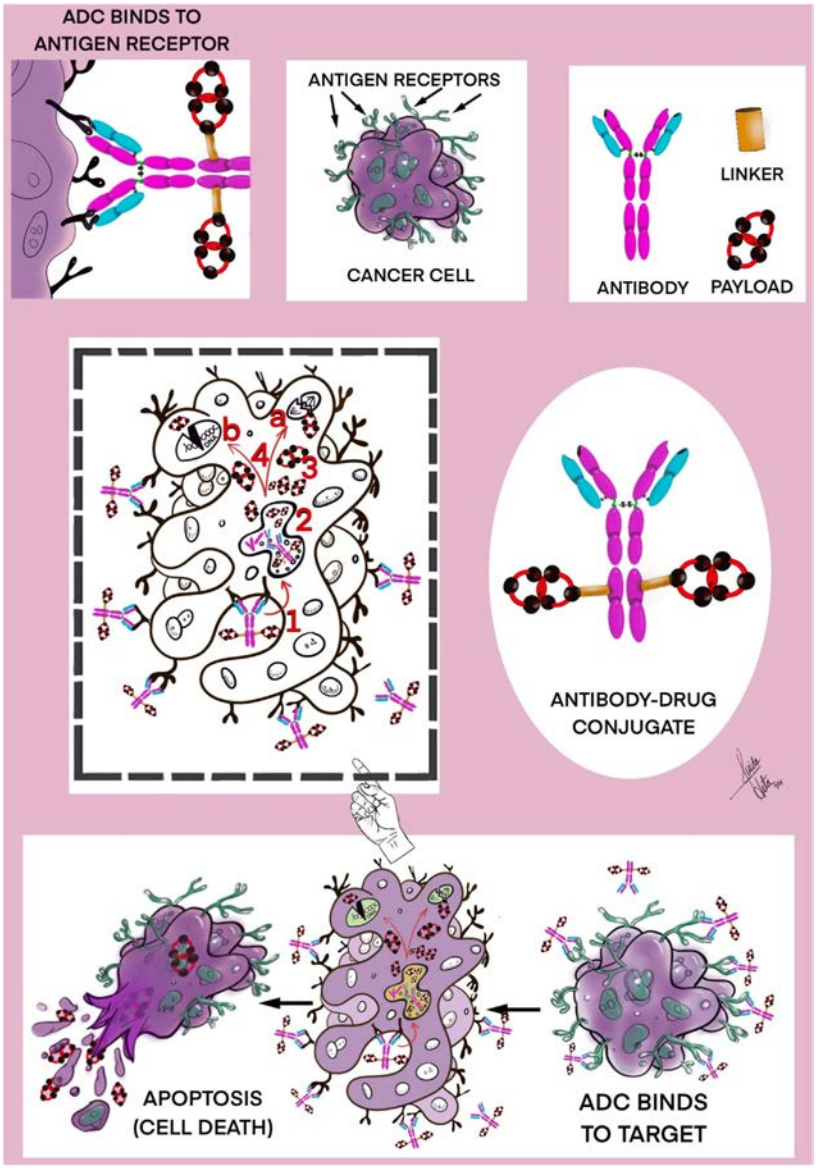

Figure. Antibody-drug conjugates are a kind of targeted antineoplastic therapy made up of 3 parts: a monoclonal antibody "guidance system" that is responsible for targeting a specific antigen, allowing attachment to the target cell, a linker molecule, and a cytotoxic drug "payload." Once the target cancer cell is tagged by the antibody, the cytotoxic compound is internalized (1) by the cancer cell into a lysosome (2), where the drug is enzymatically cleaved from the antibody and released into the cytoplasm (3). Once in the cytoplasm (4), the cytotoxic drug causes cell death (apoptosis) by either (a) microtuble disruption or (b) DNA damage.[1,3–5] Figure by Angel Guido Hita, MD.

The toxicity profile and incidence of antibody-drug conjugates are influenced by many factors. The antineoplastic effect of the targeting antibody, if any, may be changed by the attachment of linkers and payloads. The selectivity of binding to different organs/tissues versus the cancer by the targeting antibody will vary on the basis of the differential expression of the target antigens and the specificity of the antibody-antigen binding. Variations in the stability (cleavability) of the linkers in different antibody-drug conjugates will affect the leakiness of the cytotoxin to the systemic circulation. Moreover, the amount of cytotoxin attached to each molecule of the targeting antibody varies among different antibody-drug conjugates. Therefore, there may be differences in the side effect profiles of antibody-drug conjugates with the same cytotoxic payload.

With the goal of increasing awareness of these novel antineoplastic agents and their potential adverse effects seen

Table 1. Antibody-drug conjugates approved by the US Food and Drug Administration.

Antibody-Drug Conjugate Name (Trade Name)	Abbreviation	Antibody Target	Used to Treat	Common Adverse Events
DNA-damaging agents as cytotoxin				
Gemtuzumab ozogamicin (Mylotarg)	GO	CD33	Acute myeloid leukemia	Cytopenias, infection, fever, increased transaminase levels, bleeding, nausea/vomiting[6]
Inotuzumab ozogamicin (Besponsa)	InO	CD22	B-cell acute lymphocytic leukemia	Cytopenias, increased levels of aminotransferase, increased bilirubin, febrile neutropenia[7,8]
Loncastuximab tesirine (Zynlonta)	LT	CD19	Lymphoma	Cytopenias, fatigue, nausea, cough, increased gamma-glutamyl transpeptidase, diarrhea[9,10]
Fam-trastuzumab deruxtecan (Enhertu)	T-DxD	HER2	Breast cancer, gastric or gastroesophageal junction adenocarcinoma	Cytopenias (neutropenia, anemia, thrombocytopenia, leukopenia), nausea, vomiting, diarrhea, fatigue, decreased appetite, alopecia[11,12]
Antimicrotubular agents as cytotoxins				
Brentuximab vedotin (Adcentris)	BV	CD30	Certain lymphomas	Peripheral neuropathy, nausea, diarrhea, vomiting, fatigue, upper respiratory infection, cytopenias[13]
Polatuzumab vedotin (Polivy)	Pola	CD79b	Lymphoma	Peripheral neuropathy, neutropenia, anemia, thrombocytopenia, diarrhea, constipation, decreased appetite, pyrexia[14–16]
Enfortumab vedotin (Padcev)	EV	Nectin 2	Urothelial carcinoma	Peripheral sensory neuropathy, decreased appetite, diarrhea, dysgeusia, maculopapular rash, anemia[17]
Tisotumab vedotin (Tivdak)	TV	Tissue factor	Cervical cancer	Epistaxis, nausea, vomiting, fatigue, peripheral neuropathy, conjunctivitis, alopecia, constipation, decreased appetite, anemia[18–20]
Ado-trastuzumab emtansine (Kadcycla)	T-DM1	HER2	Breast cancer	Nausea, fatigue, headache, epistaxis, constipation, diarrhea, decreased appetite, elevated aspartate transferase[21]
Sacituzumab govitecan (Trodelvy)	SG	Human trophoblast cell surface Ag 22 (Trop 2)	Breast cancer, urothelial cancer	Neutropenia, diarrhea, nausea, alopecia, fatigue[22,23]
Mirevetuximab soravtansine (Elahere)	MIRV	FR alpha	Ovarian, fallopian tube, peritoneal cancer	Nausea, blurred vision, keratopathy, diarrhea, fatigue, peripheral neuropathy, dry eye[24,25]

in patients with cancer presenting to EDs, we performed a narrative review of the literature and summarized the findings. We focused on antibody-drug conjugates that are currently approved for cancer treatment in the United States and conditions that will most likely result in the need for emergency care, particularly those that mimic more common illnesses and those that are rare but serious. This paper will aid emergency physicians to recognize common presentations as potentially antibody-drug conjugate-related and increase awareness of those adverse effects that are rare but potentially serious and best treated if recognized early.

MATERIALS AND METHODS

Literature searches were performed in PubMed. Each search combined terms that mapped to antibody-drug conjugates with terms for complications. The search terms and dates are listed in Appendix E1 (available at http://www.annemergmed.com). The searches were limited to the English language. The search results were reviewed for relevance and duplication. The article bibliographies were reviewed to include additional articles as appropriate. Additionally, authors reviewed safety warnings on the package inserts and the listed adverse events in phase I to III trials of each drug. Finally, LiverTox entries, if available, were reviewed and statistics on the incidence of certain adverse events were retrieved from Merative Micromedex (https://www.micromedexsolutions.com/micromedex2/librarian).

Rare but Potentially Serious Adverse Effects

Interstitial Lung Disease and Pneumonitis. Interstitial lung disease is the most common form of drug-induced lung injury, with oncologic drugs being the most frequent cause.[55] A recent meta-analysis showed that

Table 2. Mechanisms of actions of antibody-drug conjugate payloads.

Class	Payload	Mechanism
DNA-damaging agents		
Calicheamicin	Ozogamicin	Binds to the minor groove of DNA, causing double-stranded DNA breaks[26]
Camptothecins	Deruxtecan, govitecan	Inhibits topoisomerase I, causing DNA strand breaks[12,22]
Pyrrolobenzodiazepine dimer	Tesirine (SG3199)	Alkylating agent that causes DNA interstrand crosslinks[27]
Microtubule inhibitors		
Auristatin	Vedotin (monomethyl auristatin E)	Binds to tubulin and inhibits microtubule polymerization, causing growth arrest[28]
Maytansinoid	Emtansine (DM-1)–soravtansine (DM-4)	Binds to tubulin, disrupting the microtuble assembly[29,30]

pneumonitis was the most common cause of antibody-drug conjugate-related death.[56] Trastuzumab deruxtecan (T-Dxd) causes pneumonitis in 13.58% of treated patients, with grade ≥3 in 2.19%.[57] (See Table 4 for pneumonitis symptoms and grading.) Pneumonitis was reported in 10% of patients treated with mirvetuximab soravtansine, with grade ≥3 in 1%.[58] Although phase II and III trials of enfortumab vedotin for advanced mesothelial carcinoma did not report a high incidence of pneumonitis, a retrospective analysis of the South Korean participants in these trials showed that 28% developed pneumonitis, 6.3% of which were grade ≥3.[38,59,60] In a postmarketing study of brentuximab vedotin, 3.2% of patients developed grade ≥3 interstitial lung disease, with a total incidence of 3.9%.[61] Although the incidence of interstitial lung disease and pneumonitis is <2% overall for trastuzumab emtansine (T-DM1) and tisotumab vedotin, fatal cases have been reported.[62,63]

The symptoms of interstitial lung disease and pneumonitis are nonspecific: dry cough, dyspnea on exertion, shortness of breath, fatigue, chest pain, and fever. Chest auscultation may reveal rales or crackles. Severe cases of interstitial lung disease or pneumonitis may cause hypoxia or even respiratory failure.[66]

There are no laboratory tests with high specificity to diagnose antibody-drug conjugate-related interstitial lung disease. High-resolution computed tomography (CT) is much more sensitive than chest radiography for the detection of drug-induced interstitial lung disease and should be performed whenever interstitial lung disease is in the differential diagnosis. CT findings indicative of drug-induced pneumonitis include widespread patchy consolidations, with or without intralobar reticular opacities and septal thickening.[66]

Management of interstitial lung disease and pneumonitis begins with supportive measures, including oxygen, ventilatory support as needed, and intravenous fluids. An early pulmonology consultation should be considered because the workup very likely will include bronchoscopy with bronchoalveolar lavage and/or lung biopsy.

Given that it is difficult to differentiate between infectious pneumonia and interstitial lung disease, empiric antibiotics may be indicated to cover for pneumonia until a reliable diagnosis of interstitial lung disease can be made. Treatment of antibody-drug conjugate-induced interstitial lung disease is aimed at suppressing inflammation, initially with corticosteroids. The decision to start steroids may be made in the ED, ideally in consultation with the oncologist. Patients with grade 2 pneumonitis can be administered oral steroids equivalent to 1 to 2 mg/kg prednisone per day and discharged.[55] Grade 3 toxicity is treated with oxygen as needed and prompt initiation of steroids at a dose equivalent to 1 mg/kg prednisolone per day. Grade 4 toxicity may manifest in a manner similar to that of acute respiratory distress syndrome, with severe and life-threatening symptoms. The role of the emergency physician is to resuscitate, conduct an aggressive workup, initiate corticosteroids, and intubation for mechanical ventilation if needed. Suggested regimens include 2 mg/kg methylprednisolone (or equivalent) per day or initial pulse therapy with 500 to 1,000 mg methylprednisolone per day for 3 days.[65] If there is no improvement after 48 to 72 hours, additional immune suppressants, such as infliximab, tocilizumab, mycophenolate mofetil, or intravenous immunoglobulin, may be added.[66]

Sinusoidal Obstruction Syndrome. Formerly known as veno-occlusive disease, sinusoidal obstruction syndrome is a potentially fatal syndrome that is often associated with allogenic stem cell transplantation but is also a known complication of gemtuzumab ozogamicin and inotuzumab ozogamicin (InO).[67] Damage to hepatic endothelial cells causes swelling of the sinusoids, embolization of cellular debris, and microvascular thrombosis, all of which contribute to obstruction of hepatic blood flow at the level of the hepatic sinusoid.[68]

Table 3. Incidence of adverse events with selected chemotherapeutics and antibody-drug conjugates with similar payloads.

	Incidences of Adverse Events, Overall/Grade ≥3					
Class	**Neutropenia**	**Anemia**	**Thrombocytopenia**	**PN**	**Vomiting**	**Diarrhea**
Microtubule inhibitors						
Nab-paclitaxel	73%-85%/grade ≥3: 34%-47%[31]	33%-98%/grade ≥3: 1%-28%[31]	2%-74%/grade ≥3: <1%-18%[31]	48%-54%/grade ≥3: 17%; sensory neuropathy 71%/grade ≥3: 10%[31]	12%-36%/grade ≥3: 4%-6%[31]	15%-44%[31]/grade ≥3: <1%[32]
Docetaxel	41%-100%/grade ≥3: 32%-94%[33]	67%-97%/grade ≥3: 14%-18%[33]	3%-44%[33]	Neurosensory 50%/grade ≥3: 4.1%; neuromotor 13.8%/grade ≥3: 4.0%[34]	22%-67%/grade ≥3: 4%-7%[33]	23%-78%/grade ≥3: 4%-6%[33]
Brentuximab vedotin	21%-91%/grade ≥3: 5%-82%[35]	27%-98%/grade ≥3: 4%-13%[35]	15%-41%/grade ≥3: 4%-9%[36]	45%-53%/grade ≥3: 3%-10%[36]	17%-33%/grade ≥3: 2%-3%[35]	20%-36%/grade ≥3: 1%-6%[35]
Polatuzumab vedotin	44%-60%/grade ≥3: 39%-42%[37]	28%-68%/grade ≥3: 14%-24%[37]	31%-49%/grade ≥3: 8%-40%[37]	40%-53%/grade ≥3: 1.6%-2.5%[37]	15%-27%/grade ≥3: 1.1%-2.9%[37]	31%-45%/grade ≥3: 3.9%-8%[37]
Enfortumab vedotin	Grade ≥3: 6.2%-8%[17,38]	20%-48%/grade ≥3: 2.5%-11%[39]	*	50%-67%/grade ≥3: 4%-8%[39,40]	13%-18%/grade ≥3: 2%[39]	35%-45%/grade ≥3: 2.5%-8%[39]
Tisotumab vedotin	4%-6.8%/grade ≥3: 3%-3.6%[19,41]	13%-23.2%/grade ≥3: 1%-8.4%[19,41]	Grade ≥3: 1%[19]	11%-39%/grade ≥3: 6%-7%[42]	17%-18%/grade ≥3: 1.6%-2%[42]	22%-25%/grade ≥3: 1.6%-2%[42]
Trastuzumab emtansine	7%-8% (all grades)[43]	10%-14%/grade ≥3: 1.1%-4.1%[43]	29%-31%/grade ≥3: 6%-15%[43]	21%-28%/grade ≥3: 1.6%-2.2%[43]	15%-19%/grade ≥3: 0.5%-0.8%[43]	12%-24%/grade ≥3: 0.8%-1.6%[43]
Mirvetuximab soravtansine	6.6%-13%/grade ≥3: 0%-12%[24,44]	10.7%/grade ≥3: 0.8%[24]	9.5%/grade ≥3: 0%[24]	33%-37%/grade ≥3: 2%-4%[45]	18%-19%/grade ≥3: 0%-3%[45]	29%-31%/grade ≥3: 1%-3%[45]
Topoisomerase inhibitors						
Topotecan	83%-91%/grade ≥3: 24%-80%[46]	25%/grade ≥3: 6%-42%[46]	81%/grade ≥3: 6%-30%[46]	3% (all grades)[46]	10%-40%/grade ≥3: 1%-3%[46]	6%-32%/grade ≥3: 4%-22%[46]
Irinotecan	54%-96.9%/grade ≥3: 26%-53.8%[47]	60%-97.2%/grade ≥3: 2.1%-8.4%[47]	32.6%-96%/grade ≥3: up to 4%[47]	*	44.8%-67%/grade ≥3: 3.5%-14%[47]	Early-onset 43%-51%/grade ≥3: 6.7%-8%; late-onset 72.4%-88%/grade ≥3: 23%-40%[47]
Trastuzumab deruxtecan	10%-42%/grade ≥3: 5%-19.1%[11,48]	31%-58%/grade ≥3: 7%-38%[49]	20%/grade ≥3: 3.4%[49]	13%/grade ≥3: 0.4%[49]	26%-49%/grade ≥3: 1.6%-3.8%[49]	19%-32%/grade ≥3: 1%-2.4%[49]
Sacituzumab govitecan	64%/grade ≥3: 43%-58%[50]	33%-50%[22,23]/grade ≥3: 9%-21%[50]	9%/grade ≥3: 6%[50]	12%[50]	23%-49%/grade ≥3: 1%-6%[50]	59%-72%/grade ≥3: 9%-12%[50]
Agents that cause interstrand DNA crosslinks						
Cisplatin	*	11%[51]	16%[51]	Common	Up to 100%[51]	*

Loncastuximab tesirine	40% grade ≥3: 26%[9]	26% grade ≥3: 10%[9]	33%/grade ≥3: 18%[9]	3%/grade ≥3: 1%[9]	13%/grade ≥3: 0%[9]	17%/grade ≥3: 2%[9]
Agents that cause DNA double-strand breaks						
Doxorubicin	Common, dose-dependent[52]	*	Grade ≥3: 0.1%[52]	Has been reported[52]	34%-37%[52]	*
Gemtuzumab ozogamicin	Grade ≥3: 2%-3%[53]	*	Grade ≥3: 19%-35%[53]	*	21%[53]	Grade ≥3: 2%-5%[53]
Inotuzumab ozogamicin	49% grade ≥3: 40%-49%[54]	35%-45% grade ≥3: 24%-48%[54]	51% grade ≥3: 42%-45%[54]	*	15%-45%[54]	11%[54]

PN, Peripheral neuropathy.
*Not reported in Merative Micromedex.

In a phase III trial of gemtuzumab ozogamicin for acute myeloid leukemia, the incidence of sinusoidal obstruction syndrome was 4.6% in the gemtuzumab ozogamicin arm.[65,69] In a phase III trial of InO for relapsed/recurrent acute lymphoblastic leukemia, sinusoidal obstruction syndrome occurred in about 13% of InO-treated patients.[70]

Weight gain, often rapid, is the earliest symptom of sinusoidal obstruction syndrome. Edema, ascites, jaundice, and painful hepatomegaly are also common. Severe sinusoidal obstruction syndrome may cause pleural effusions, pulmonary infiltrates, hypoxia, encephalopathy, thrombocytopenia, and renal insufficiency or failure.[71]

Laboratory workup shows elevation of bilirubin and transaminases and possibly thrombocytopenia and/or renal dysfunction. Ultrasound may reveal ascites, hepatomegaly, and attenuated or reversed hepatic venous flow. Gallbladder wall thickening is less specific but also suggestive in the correct context.[68]

Fluid and electrolyte management should be started in the ED without waiting for a definitive diagnosis. Fluid overload is treated first with gentle diuresis with furosemide or spironolactone.[68] Respiratory distress due to ascites may be treated with paracentesis, limiting the paracentesis volume to 1 L at a time to protect the kidneys.[72] If fluid overload cannot otherwise be controlled, hemodialysis or hemofiltration may be necessary. A transjugular intrahepatic portosystemic shunt may also provide relief, but it is often transitory.

The only medication with proven benefit in sinusoidal obstruction syndrome is defibrotide. Its benefits include stabilization of the endothelium, a decrease in vascular permeability, and a profibrinolytic and antithrombotic effect without acting as a systemic anticoagulant.[73] Defibrotide, at a dose of 6.25 mg/kg every 6 hours, should be started immediately for severe sinusoidal obstruction syndrome and can be used for mild or moderate sinusoidal obstruction syndrome that worsens or does not improve within 2 days of supportive therapy (see Table 5 for sinusoidal obstruction syndrome severity grading). Treatment is continued for 21 days.[72]

Progressive Multifocal Leukoencephalopathy. Progressive multifocal leukoencephalopathy is an often fatal demyelinating viral infection of the central nervous system caused by the John Cunningham virus. Progressive multifocal leukoencephalopathy has been associated with several antibody-based therapies, and both brentuximab vedotin and polatuzumab vedotin (Pola) carry warnings for an association with progressive multifocal leukoencephalopathy. There was a single death due to progressive multifocal leukoencephalopathy in Pola's pivotal

Table 4. Pneumonitis grading and ED management.

CTCAE* Grade[64]	Description[55,64]	ED Management
1	Asymptomatic – may be seen in ED incidentally on imaging	Inform treating oncologist, no ED intervention
2	Symptomatic, requiring medical intervention; dyspnea, asthenia, chest pain, nonproductive cough; may have tachypnea, crackles, or fever; PaO_2 less than baseline but >60 mmHG and not requiring oxygen	Oral corticosteroids, equivalent to 1-2 mg/kg prednisone per day; discharge[55]
3	Severe symptoms limiting self-care activities of daily living; dyspnea, asthenia, chest pain, nonproductive cough, tachypnea, crackles, possibly fever and cyanosis, SpO_2 altered, PaO_2 <60 mmHg	Oxygen, admission, prednisolone 1 mg/kg per day or equivalent[55]
4	Life-threatening respiratory compromise; urgent intervention indicated; presentation similar to grade 3 but with severe hypoxemia and respiratory distress	Resuscitation, possibly including high-flow oxygen or intubation; aggressive workup; steroids: 2 mg/kg methylprednisilone or equivalent per day or initial pulse therapy with 500-1000 mg methylprednisilone per day[55,65]
5	Death	-

*Common Terminology Criteria for Adverse Events.

trial.[75] There have been case reports of progressive multifocal leukoencephalopathy in patients treated with brentuximab vedotin, with an incidence of <0.1% in clinical trials and postmarket reporting.[76–79]

The varied presentation of progressive multifocal leukoencephalopathy reflects its diffuse and multifocal central nervous system involvement. Progressive multifocal leukoencephalopathy may start with speech dysfunction, motor dysfunction, cognitive deficits, visual deficits, or gait dysfunction. This is followed by progressive neurologic deterioration over weeks to months.

CT of the brain may show subcortical densities. Magnetic resonance imaging is much more sensitive and may show areas of demyelination without significant edema.[80] Lesions are hyperintense on T2 and FLAIR sequences and hypointense on T1. If a lumbar puncture is performed to assess for other causes, a polymerase chain reaction for the John Cunningham virus can aid in diagnosis.[81]

Unfortunately, an effective treatment for controlling or reversing progressive multifocal leukoencephalopathy has not yet been found. Treatment is largely supportive, with a focus on restoring immune function where possible.

Neurologic Complications. Orsini et al[82] reported a case of a 13-year-old girl who developed a posterior reversible encephalopathy syndrome–like illness while receiving brentuximab vedotin monotherapy. A retrospective review of patients treated with brentuximab vedotin reported 11 cases of severe inflammatory demyelinating polyradiculopathies, causing mild distal sensory symptoms that progressed to a Guillain-Barre–like syndrome, including severe motor deficit and sensory ataxia.[83] Finally, T-DM1 was the suspected cause of neurotoxic damage to the nucleus of the abducens nerve in the pons, which presented as blurred vision, diplopia, and esotropia.[84]

Adverse Effects Associated With the Antibody Component of Antibody-Drug Conjugates

Infusion-Related Reactions. Antibody-drug conjugate infusion may cause acute symptoms, including anaphylactoid reactions with rash, dyspnea, and hypotension.[85] Symptoms vary by drug but may include fever, chills, dyspnea, rash, nausea/vomiting, abdominal pain, hypoxia, pruritus, hypotension, tachycardia, and dizziness.[18,86–88] Most reactions occur within 30 to 120 minutes of infusion, but severe or delayed reactions may present to the ED.[85]

In a trial of patients receiving brentuximab vedotin in combination with bendamustine (an alkylating agent), 43.6% of patients had a delayed (>24 hours after infusion) reaction, characterized by fever, generalized maculopapular rash, chills, nausea, and pruritis; 12.7% of these were grade 3 reactions. Infusion-related reactions occurred in 12.7% of patients receiving brentuximab vedotin alone, so it is possible that these reactions cannot be solely attributed to brentuximab vedotin.[89]

Anaphylactoid reactions are clinically indistinguishable from true anaphylaxis, and the treatment is the same, with antihistamines, corticosteroids, intravenous fluids, H_2-

Table 5. Sinusoidal obstruction syndrome severity grading, per European Society of Marrow and Blood Transplantation criteria.[74]

Variable	Mild	Moderate	Severe	Very Severe – Multiorgan Dysfunction or Failure
Time since first clinical suspicion of sinusoidal obstruction syndrome*	>7 d	5-7 d	≤4 d	Any time
Bilirubin (mg/dL)	≥2 and <3 d	≥3 and <5 d	≥5 and <8 d, or doubling within 48 h	≥8 d
Transaminases	≤2× normal	>2× and ≤5× normal	>5× and ≤8× normal	>8× normal
Weight increase	<5%	≥5% and <10%	≥5% and <10%	≥10%
Renal function	<1.2× baseline*	≥1.2 and <1.5× baseline	≥1.5 and >2× baseline	≥2× baseline or other signs of multiorgan dysfunction or failure

*European Society of Marrow and Blood Transplantation criteria specify baseline at time of stem cell transplant.

receptor blockers, and epinephrine.[85] Other symptoms are managed with supportive care.

Cardiovascular Toxicities. Although it is well known that trastuzumab may cause cardiotoxicity or reversible cardiomyopathy, studies of the antibody-drug conjugates that use trastuzumab as the targeting antibody (eg, T-DM1 and T-Dxd) have shown lower rates of cardiotoxicity than those observed with trastuzumab alone.

A meta-analysis of studies of T-Dxd reported a 1.95% incidence of decreased left ventricular ejection fraction and a 7.7% incidence of heart rate corrected QT interval prolongation. Grade 3 decrease in left ventricular ejection fraction and grade 3 heart rate corrected QT interval prolongation both had incidence rates of <1%; no higher grades were reported.[90] A pooled analysis of 1,961 patients treated with T-DM1 showed an incidence of cardiac events of 3.37%, including a small number of grade 3 events and arrhythmias.[91] Another meta-analysis of T-DM1-associated adverse events reported a 1.9% incidence of grade ≥3 hypertension.[92]

Gemtuzumab ozogamicin has been associated with reduced left ventricular ejection fraction, and cases of symptomatic congestive heart failure in the pediatric population have been reported.[93,94] Clinical trials and studies in adults have not detected statistically significant increases in cardiac adverse events for gemtuzumab ozogamicin.[26,69,95,96] The package insert for gemtuzumab ozogamicin notes that in one study, cardiac adverse events occurred at a similar rate in the study and control populations.[97] In some studies, patients experienced tachycardia or reversible dysrhythmias; however, the sample sizes of these studies were relatively small.[6,98,99] Meta-analysis and pharmacovigilance studies may be indicated.

Overall, cardiovascular toxicity from antibody-drug conjugates is rare but should be considered in patients who present with congestive heart failure or arrhythmia. To our knowledge, there is currently no treatment recommendation that is specific for antibody-drug conjugate-related cardiotoxicity.

Adverse Effects Associated With Cytotoxin Moiety of Antibody-Drug Conjugates

Hepatoxicities. Many antibody-drug conjugates have been associated with hepatic dysfunction, most commonly in the form of elevated transaminases, bilirubin, or other liver chemistries. Severe liver dysfunction and liver failure have been seen during or after treatment with gemtuzumab ozogamicin, InO, T-DM1, and brentuximab vedotin.[6,7,79,92,100–102] A pharmacovigilance study detected signals that demonstrated an association between T-DM1, enfortumab vedotin, brentuximab vedotin, Pola, GO, InO, and T-Dxd and drug-induced liver injury.[103]

In clinical trials, some patients developed abnormal liver chemistries after receiving T-Dxd, sacituzumab govitecan, loncastuximab tesirine, mirvetuximab soravtansine, and Pola, but these were usually transient and asymptomatic.[9,11,22,24,104]

When abnormal liver function tests are found, the oncologist should be informed immediately if sinusoidal obstruction syndrome is likely, and the patient should be admitted for further evaluation and management. Even in the absence of concern for sinusoidal obstruction syndrome, elevation of transaminases to >20 times the upper limit of normal, or with concurrent jaundice, also requires expedited workup and prompt consultation with the oncologist and a hepatologist.[102,105–107] For a moderate elevation, ie, one that is 5 to 15 times the upper limit of normal, outpatient follow-up is appropriate as long as the patient is asymptomatic and without jaundice.[100,102,105–111] The patient should follow up with the oncologist in the next few days in case dose delays or reductions are needed.

Table 6. Diarrhea severity grading and management.

Severity Grade[64]	Criteria[64]	Treatment[127]
1	Increase of ≤4 stools/d or mild increase in ostomy output over baseline	Oral hydration, loperamide, diet modification
2	Increase of 4-6 stools or moderate increase in ostomy output over baseline; limits instrumental activities of daily living	As above, consider addition of intravenous hydration and octreotide
3	Increase of ≥7 stools/d or severe increase in ostomy output over baseline; hospitalization indicated, limits self-care activities of daily living	Intravenous hydration, octreotide (100-150 μg subcutaneously or 25-50 μg/h), monitoring and repletion of electrolytes, hospitalization
4	Life-threatening consequences, urgent intervention indicated	Octreotide, aggressive resuscitation, hydration, electrolyte replacement
5	Death	

Peripheral Neuropathy. Peripheral neuropathy is a common adverse effect of many antineoplastic agents, especially DNA-damaging agents and microtubule inhibitors (Table 3). Peripheral neuropathy is seen most frequently with antibody-drug conjugates that contain vedotin, which is the microtubule inhibitor monomethylauristatin E. The incidence rates of peripheral neuropathy appear to be lower than those with representative antineoplastic agents with similar mechanisms to the cytotoxins in antibody-drug conjugates, although they remain quite high. Most cases of peripheral neuropathy due to brentuximab vedotin improve or resolve after treatment with brentuximab vedotin is stopped.[112] Duloxetine has been shown to decrease both pain and nonpainful symptoms of peripheral neuropathy, such as numbness and tingling, and it is the only pharmacologic treatment recommended by the American Society of Clinical Oncology guidelines.[113]

Hematologic Toxicities. Neutropenia, anemia, and thrombocytopenia are common and well-known consequences of both cancer therapies and cancer itself. All antibody-drug conjugates that are currently on the market have an association with at least one cytopenia.[9,11,12,14,17,19–21,24,44,93,114–117] Emergency care consists of transfusions as needed for anemia or thrombocytopenia and workup and treatment for neutropenic fever/neutropenia-related infections.

Hemorrhage. Both tisotumab vedotin and T-DM1 are associated with bleeding, which is fortunately mostly minor. In a phase II trial, 39% of patients receiving tisotumab vedotin had bleeding related to treatment; 2 patients had grade 3 bleeding (one rectal hemorrhage and one cystitis hemorrhage).[19] Epistaxis and vaginal bleeding were the most common bleeding events in both this and a subsequent phase III trial.[41] In the latter, there was a 26% incidence of epistaxis in the tisotumab vedotin arm (none severe) and a 10% overall incidence of vaginal bleeding (1.2% grade ≥3).[41] Clinical trials of T-DM1 have reported epistaxis rates of 17% to 31% and serious bleeding in 0.4% to 4% of treated patients.[118–120]

There are several case reports of intracranial hemorrhage or expanding hematoma in patients receiving T-DM1 with a history of radiation therapy for brain metastasis.[121–123]

Severe bleeding (grade ≥3) related to thrombocytopenia occurs in 7% to 21% of patients treated with gemtuzumab ozogamicin, including intracranial hemorrhages.[6,69,98] Thrombocytopenia-related bleeding is seen in 33% to 42% of patients treated with InO; the rate of grade ≥3 hemorrhage is about 5%.[13]

Gastrointestinal Toxicities. Vomiting and diarrhea very often result in ED visits, particularly in those undergoing cancer treatment.[124] Diarrhea is a common side effect of antibody-drug conjugates, with an incidence of >20% in patients treated with brentuximab vedotin, T-DM1, Pola, enfortumab vedotin, T-Dxd, sacituzumab govitecan, tisotumab vedotin, and mirvetuximab soravtansine.[11,12,14,15,17-24,38,44,48,114,116,117,125] Sacituzumab govitecan was particularly notable for causing grade ≥3 diarrhea in 10% of recipients, making them much more likely to require emergency care (Table 6).[23,117] Vomiting occurs in more than 20% of those treated with brentuximab vedotin, T-Dxd, sacituzumab govitecan, tisotumab vedotin, and mirvetuximab soravtansine.[11,12,18,20,23,24,44,117,126] Because each of these antibody-drug conjugates is also associated with a high incidence of diarrhea, patients may need vigorous intravenous hydration and electrolyte replacement in addition to antiemetics. Constipation is seen in more than 20% of patients treated with gemtuzumab ozogamicin, T-DM1, PV, T-Dxd, sacituzumab govitecan, and tisotumab vedotin.[6,12,14,18,20,21,116,117]

A pharmacovigilance study in 2022 confirmed that there is a strong association between brentuximab vedotin and pancreatitis; whereas its exact incidence is not known, it is low.[128] Case reports include a pediatric patient and 2 patients who died from pancreatitis.[129–131] ED workup and

Table 7. Incidence of ocular adverse effects with use of antibody-drug conjugates.*

Adverse Event	Antibody-Drug Conjugate	Overall Incidence	Incidence Grade ≥3
Dry eye	EV	15.9%-23%[59,113]	None[17,38]
	TV	13.2%-23%[19,41]	None[19,41]
	MIRV	41%-57%[25,44]	2%-3.2%[25,44]
Blurred vision	EV	4.1%-15%[17,38]	None[17,38]
	MIRV	41%-57%[25,142]	1%-7.8%[25,142]
Conjunctivitis	TV	26%-31.2%[19,41]	None[19,41]
Keratitis	TV	11%-15.6% [19,41]	None[19,41]
Keratopathy	MIRV	32.1%-34%[25,142]	0%-9%[25,142]
Corneal disorder	EV	0.7%[17]	None[17]

Phase III studies have not reported ocular adverse events.[118–120,143]
Ocular adverse events are not frequently reported for GO, BV, InO, Pola, T-Dxd, SG, and LT.
EV, enfortumab vedotin; *GO*, gemtuzumab ozogamicin; *LT*, loncastuximab tesirine; *MIRV*, mirevetuximab soravtansine.
*Phase I and II studies of T-DM1 reported ocular adverse events, most commonly dry eye, increased lacrimation, blurred/impaired vision, and conjunctivitis, in 10%-31% of treated patients.[29,144]

treatment for antibody-drug conjugate-associated pancreatitis do not differ from the standard-of-care for emergency pancreatitis. A fasting triglycerides test is indicated because brentuximab vedotin-induced hypertriglyceridemia has been reported to cause pancreatitis.[132]

Tumor Lysis Syndrome. Tumor lysis syndrome is an oncologic emergency caused by the release of large amounts of intracellular contents, resulting in hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia. It can occur spontaneously but is most often treatment-related.[133] Gemtuzumab ozogamicin, Pola, and brentuximab vedotin all carry package insert warnings that they may cause tumor lysis syndrome. Across the 3 phase II trials cited in the 2000 US Food and Drug Administration approval summary of gemtuzumab ozogamicin, there were 4 cases of tumor lysis syndrome, including one fatality.[134] A phase II study of brentuximab vedotin reported that one patient developed tumor lysis syndrome, for an incidence of 1.7%. A systematic review in 2016 showed no additional cases among published phase I to III clinical trials.[114,135]

Adverse Effects Not Associated With Antibodies or the Pharmacologic Class of Cytotoxins

Ocular Toxicities. Vision-threatening toxicities are rare; however, ocular adverse effects are frequently reported with several antibody-drug conjugates (Table 7). Clinical trials of brentuximab vedotin did not report significant ocular adverse events, but there are 3 case reports of uveitis associated with brentuximab vedotin use.[136–141]

Keratitis induced by antibody-drug conjugates is initially treated with topical corticosteroids and referral to an ophthalmologist. Uveitis requires topical and possibly also systemic corticosteroids. An urgent ophthalmology consultation is indicated if uveitis is suspected, and hospital admission may be necessary.[145] In the event that an ocular condition is suspected of being due to an antibody-drug conjugate, the oncologist should be informed because a dose reduction or treatment pause may be indicated.[146]

Dermatologic Toxicities.

Skin Rash

Skin rash is a very common side effect of several antibody-drug conjugates, affecting more than 10% of patients during treatment with T-DM1, enfortumab vedotin, brentuximab vedotin, tisotumab vedotin, Pola, gemtuzumab ozogamicin, or loncastuximab tesirine.[9,15,18,21,69,125,147] These rashes are generally well tolerated and require only comfort measures, such as topical carticosteroids and antihistamines.

Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome

There are case reports of Stevens-Johnson syndrome/toxic epidermal necrolysis associated with enfortumab vedotin, tisotumab vedotin, and brentuximab vedotin, but its true incidence is not known.[41,148,149] Stevens-Johnson syndrome and toxic epidermal necrolysis are well known to emergency clinicians, and when they are related to antibody-drug conjugates, the treatment is no different from standard of care.

Hand-Foot Syndrome

Hand-foot syndrome is a toxic erythema of chemotherapy syndrome, also known as palmar-plantar erythrodysesthesia syndrome, acral erythema, and Burgdorf syndrome. It occurs in around 1% of patients treated with

T-DM1.[21,143] There is also a case report of hand-foot syndrome in a patient treated with brentuximab vedotin.[150]

Patients present with palmoplantar numbness, tingling, or burning pain and sharply demarcated erythema (or hyperpigmentation in people of color), with or without edema, cracking, or desquamation. In advanced stages, there may be blistering and ulceration. Although sometimes painless, hand-foot syndrome can be very painful.[151]

Data on the guidance of therapy are very limited. Symptomatic treatments include COX-2 inhibitors, vitamin E, oral corticosteroids, and analgesics. Topical therapies include emollients, topical corticosteroids, keratolytics, and topical sildenafil. A dose reduction may be considered by the oncologist.[151]

Spider Telangiectasias

T-DM1 has been associated with the development of spider telangiectasias in case reports. This is an asymptomatic skin rash, but patients may present to the ED if mucosal telangiectasias leads to epistaxis or other bleeding.[152,153] There is also a case report of pulmonary arterial hypertension associated with telangiectasias that developed while the patient was receiving T-DM1.[154]

Effusions and Peripheral Edema. Loncastuximab tesirine may cause peripheral edema (incidence of 20%, severe 1%), pleural effusions (incidence of 10%, severe in 2%), or pericardial effusions (incidence of 3%, severe in 2%).[9] Spironolactone and dose delays/reductions are used for prevention and treatment.[27] There is also a case report of symptomatic pleural and pericardial effusion attributed to T-DM1.[155]

Peripheral edema has also been reported after treatment with sacituzumab govitecan, brentuximab vedotin, and enfortumab vedotin.[38,117,125,126,156]

Hyperglycemia. Four percent to 6% of patients treated with enfortumab vedotin develop severe hyperglycemia.[157,158] Across the trials on which US Food and Drug Administration approval was based, there were 3 cases of diabetic ketoacidosis, including one fatality.[158] Two cases were in patients with no history of diabetes.[158] Hyperglycemia has also been reported in patients receiving Pola and brentuximab vedotin, including care reports of diabetic ketoacidosis with brentuximab vedotin.[15,116,159–161] Although hyperglycemia has been observed with other antibody-drug conjugates, the incidence is low, or the link is less clear due to coadministration of other drugs.[18,48,162]

Emergency workup and treatment are no different from those in other hyperglycemic patients and should focus on hydration, attention to electrolytes, and insulin as needed.

FURTHER RESEARCH

The true incidence of many antibody-drug conjugate toxicities is unknown, especially for recently approved antibody-drug conjugates. No clinical studies have assessed the prevalence of adverse effects of antibody-drug conjugates for which patients with cancer present to the ED. The ability of antibody-drug conjugates to deliver highly toxic chemotherapy in a targeted manner has reduced the incidence of off-target side effects, widening the therapeutic window to achieve higher on-target effects. Theoretically, high on-target efficiency may increase the risk for tumor lysis syndrome, but postmarketing pharmacovigilance research is needed to study this. Further investigations could include the real-world incidence of serious bleeding with tisotumab vedotin and T-DM1, diabetic ketoacidosis with enfortumab vedotin, or Stevens-Johnson syndrome with enfortumab vedotin, and brentuximab vedotin.

In conclusion, although antibody-drug conjugates offer significant benefits for patients with cancer, their expanding use presents a challenge for emergency physicians. Common ED complaints, such as red eye, rash, vomiting, diarrhea, or hyperglycemia, often need only standard-of-care treatment. Nevertheless, recognition that the patient has received an antibody-drug conjugate should prompt communication with the oncologist and raise the level of suspicion for severe illness. This vigilance can facilitate prompt diagnosis and potentially life-saving interventions for complications such as diabetic ketoacidosis, pancreatitis, tumor lysis syndrome, and Stevens-Johnson syndrome. Furthermore, knowledge of specific antibody-drug conjugate toxicities can guide diagnostic workup. For instance, respiratory complaints in patients treated with T-Dxd or mirvetuximab soravtansine warrant a CT scan to assess for interstitial lung disease, whereas workup of dyspnea in a patient on loncastuximab tesirine might include an ultrasound to look for pleural or pericardial effusion. Similarly, weight gain or ascites in patients receiving gemtuzumab ozogamicin or InO warrants evaluation for sinusoidal obstruction syndrome. Heightened awareness of potential severe complications and familiarity with specific antibody-drug conjugate toxicities are essential to emergency physicians for the delivery of optimal care.

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