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CONTRAST-ENHANCED ULTRASOUND (CEUS) IN CHILDREN

Contrast-enhanced ultrasound: a comprehensive review of safety in children

Aikaterini Ntoulia[1] · Sudha A. Anupindi[1,2] · Susan J. Back[1,2] · Ryne A. Didier[1,2] · Misun Hwang[1,2] · Ann M. Johnson[1,2] · M. Beth McCarville[3] · Frederica Papadopoulou[4] · Maciej Piskunowicz[5] · Maria E. Sellars[6] · Kassa Darge[1,2]

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Abstract

Contrast-enhanced ultrasound (CEUS) has been increasingly used in pediatric radiology practice worldwide. For nearly two decades, CEUS applications have been performed with the off-label use of gas-containing second-generation ultrasound contrast agents (UCAs). Since 2016, the United States Food and Drug Administration (FDA) has approved the UCA Lumason for three pediatric indications: the evaluation of focal liver lesions and echocardiography via intravenous administration and the assessment of vesicoureteral reflux via intravesical application (contrast-enhanced voiding urosonography, ceVUS). Prior to the FDA approval of Lumason, numerous studies with the use of second-generation UCAs had been conducted in adults and children. Comprehensive protocols for clinical safety evaluations have demonstrated the highly favorable safety profile of UCA for intravenous, intravesical and other intracavitary uses. The safety data on CEUS continue to accumulate as this imaging modality is increasingly utilized in clinical settings worldwide. As of August 2021, 57 pediatric-only original research studies encompassing a total of 4,518 children with 4,906 intravenous CEUS examinations had been published. As in adults, there were a few adverse events; the majority of these were non-serious, although very rarely serious anaphylactic reactions were reported. In the published pediatric-only intravenous CEUS studies included in our analysis, the overall incidence rate of serious adverse events was 0.22% (10/4,518) of children and 0.20% (10/4,906) of all CEUS examinations. Non-serious adverse events from the intravenous CEUS were observed in 1.20% (54/4,518) of children and 1.10% (54/4,906) of CEUS examinations. During the same time period, 31 studies with the intravesical use of UCA were conducted in 12,362 children. A few non-serious adverse events were encountered (0.31%; 38/12,362), but these were most likely attributable to the bladder catheterization rather than the UCA. Other developing clinical applications of UCA in children, including intracavitary and intralymphatic, are ongoing. To date, no serious adverse events have been reported with these applications. This article reviews the existing pediatric CEUS literature and provides an overview of safety-related information reported from UCA uses in children.

Keywords Adverse events · Adverse reactions · Children · Contrast-enhanced ultrasound · Intracavitary · Intravenous · Intravesical · Safety · Ultrasound · Ultrasound contrast agents

✉ Aikaterini Ntoulia
ntouliaa@chop.edu

[1] Department of Radiology, Children's Hospital of Philadelphia, 3401 Civic Center Blvd., Philadelphia, PA 19104, USA

[2] Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

[3] Department of Diagnostic Imaging, St. Jude Children's Research Hospital, Memphis, TN, USA

[4] Pediatric Ultrasound Center, Thessaloniki, Greece

[5] Department of Radiology, Medical University of Gdansk, Gdansk, Poland

[6] Department of Radiology, King's College Hospital, London, UK

Introduction

Contrast-enhanced ultrasound (CEUS) imaging with the use of second-generation ultrasound contrast agents (UCAs) is increasing worldwide. The United States Food and Drug Administration (FDA) approved the UCA Lumason (Bracco Diagnostics, Monroe Township, NJ) for three pediatric indications: evaluation of focal liver lesions and pediatric echocardiography via intravenous administration and evaluation of vesicoureteral reflux via intravesical application. Outside the United States, Lumason is known as SonoVue (Bracco, Milan, Italy). SonoVue has been approved for pediatric intravesical applications in Europe and China. Two other currently available second-generation UCAs, Optison (GE Healthcare, Princeton, NJ) and Definity (Lantheus, North Billerica, MA), have not been approved for a pediatric indication, but there are reports of their off-label use in children.

Before Lumason/SonoVue received pediatric approval, all CEUS applications in children were performed off-label. The term "off-label" refers to the use of a licensed medical product for either an indication, or in a population, or via a route of administration that is different from those specified in the package insert. This practice is acceptable when it is clinically appropriate (reasonable and necessary) and based upon sound scientific evidence or sound medical judgment.

The groundwork regarding the safety and efficacy of the intravenous applications of UCA in children was predominantly based on the experience with the use of SonoVue in adults. In 2001, SonoVue was approved in Europe for specific intravenous applications in adults: cardiac, liver, breast and vascular. In 2003, SonoVue was approved in China for the same applications in adults. In the early years of CEUS implementation, large-scale studies including several thousand intravenous injections of SonoVue in adults demonstrated its high safety profile and reported few adverse events. One of the earliest large-scale safety studies of CEUS was published in 2006 and described the intravenous use of SonoVue for abdominal applications in adults. Data from a total of 23,188 intravenous CEUS examinations in adults were collected retrospectively from 28 Italian centers and analyzed; in this study, the overall rate for all adverse events was 0.13% (29/23,188) and for serious adverse events was <0.01% (2/23,188) [1].

Two recent large-scale single-center retrospective studies demonstrated similar findings. Both studies took place in China with the intravenous use of SonoVue for CEUS applications to abdominal and superficial organs (thyroid, breast, lymph nodes) [2, 3]. The first study included 30,222 adults. The overall incidence rate of adverse events was 0.02% (6/30,222) and <0.01% (2/30,222) for serious adverse events, including 2 cases of anaphylactic shock [2]. The second study included 34,478 intravenous CEUS examinations in adults. In total, 40 adverse reactions were identified (0.12%), with 3 cases of anaphylactic shock (<0.01%) reported [3]. In both studies, the non-serious adverse events reported were predominantly mild in severity and were analogous to what is described in the product label [4].

In children, smaller studies reported similar results regarding the safety of UCA for the two most common pediatric uses (intravenous and intravesical). Since second-generation UCAs became available in the early 2000s, 57 pediatric-only original research studies encompassing a total of 4,518 children with 4,906 intravenous CEUS examinations have been published [5–61]. As in adults, there were a few adverse events; the majority of these were non-serious, although very rarely serious anaphylactic reactions were reported. During the same time period, 31 studies with the intravesical use of UCA were conducted in 12,362 children [6, 62–91]. A few minor adverse events were encountered, but these were most likely attributable to the bladder catheterization rather than the UCA. Other evolving clinical applications of UCA in children, including intracavitary and intralymphatic, are ongoing. To date, no serious adverse events have been reported with these applications [92–98].

Among these studies in children, two reports based on the experience in European centers, the European pediatric CEUS survey and the pediatric registry of the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) presented cumulative safety data from the use of SonoVue [5, 6]. In 2012, the European pediatric CEUS survey reported safety data from 45 centers regarding the pediatric intravenous and intravesical uses of SonoVue [6]. Of a total of 948 intravenous CEUS examinations, 5 children were reported to experience 6 minor adverse events (0.53%). No adverse events were recorded in 4,131 intravesical examinations [6]. In 2021, the pediatric registry of EFSUMB reported safety data contributed from 19 centers on the intravenous use of SonoVue [5]. In this registry, which encompassed 1,676 children who underwent CEUS with intravenous administration of SonoVue, 19 children (1.1%) experienced adverse events; 4 children developed severe, 5 moderate and 6 mild hypersensitivity reactions, and 4 children had mild symptoms other than hypersensitivity reactions. The design of the survey and registry suggests that there was overlap in the number of children that they reported and the number of children included in the original research studies that were published by the contributing institutions and centers. Nevertheless, both reports provide substantial evidence to support the high safety profile of SonoVue in children [5, 6].

Compared to other contrast agents that are routinely used in pediatric radiology, e.g., iodinated contrast agent and

gadolinium, UCAs have a very low incidence of adverse events, particularly serious adverse events. One study including 11,306 intravenous injections of low-osmolality nonionic iodinated contrast media in children and neonates documented an allergic-like reaction rate of 0.18% [99]. Two studies including 13,344 and 15,706 injections of gadolinium-based contrast agents in children documented allergic-like reaction rates of 0.04% and 0.05%, respectively [100, 101]. Another safety advantage is that UCAs are not excreted by the kidneys and therefore are not nephrotoxic. They can be safely used in children with renal impairment without the need for laboratory tests prior to administration. They are also not associated with the risk of nephrogenic systemic fibrosis or tissue deposition. Furthermore, CEUS exams do not require sedation and can be performed in different settings, including at the bedside and in the operating room.

As CEUS use increases in pediatric clinical settings, there is ongoing accumulation of safety data, and thereby knowledge about its safety profile is continually evolving. The aim of this article is to review the pediatric CEUS literature and provide an overview of safety-related information reported on the intravenous, intravesical, and developing uses of UCAs in children. Pediatric radiologists, sonographers and medical staff who perform CEUS should be aware of the types of possible adverse events and be prepared to recognize the signs and symptoms and provide appropriate management.

Terminology pertaining to adverse events

To standardize the terminology used to report adverse events, various regulatory authorities, safety data registries, and major terminology initiatives have developed comprehensive resources. While there might be variations in the terminology used in specific contexts (e.g., oncology), common concepts and standard definitions pertain in most settings. The definitions of adverse events we present here are in accordance with the FDA Code of Federal Regulations and World Health Organization resources [102, 103]. Note that these definitions use the term "drug" to refer to all medical or pharmaceutical products, including UCAs. An "adverse event" is defined as any unwanted medical occurrence associated with the use of a drug in humans, whether or not it is considered drug-related [102]. That includes any undesired sign (including laboratory findings), symptom, or disease that occurs during the use of a medical product, even if they are not related to that product. The term "adverse event" is often used interchangeably with the terms "side effect" and "adverse reaction," although this usage is not always correct. "Side effect" is an unintended effect that occurs with a normal dose of the drug related to its pharmacological properties [103]. The term "side effect" has been used in various ways, usually to describe negative (unfavorable) effects, but also positive (favorable) effects [104]. Side effects can be well known and even expected and require no change in patient management. It is recommended that this term should no longer be used and particularly should not be regarded as synonymous with adverse event or adverse reaction [105]. An "adverse reaction" is a response to a drug that is noxious and unintended, and occurs at doses normally used for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function [103]. The definition of "adverse reaction" is limited to those adverse events for which there is reasonable evidence to suggest that there is a causal relationship between the drug and the event. Therefore, adverse reactions are a subset of adverse events. It is adverse events that are recorded during clinical trials.

Adverse events are classified according to their seriousness and severity (i.e. intensity). The seriousness of an adverse event relates to its outcome and is a regulatory definition. A "serious adverse event" occurs at any dose and results in any of the following outcomes: death, a life-threatening event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Adverse events might also be considered serious if they jeopardize the patient or subject and require medical or surgical intervention to prevent one of the outcomes listed in this definition. An example of such medical events is allergic bronchospasm requiring intensive treatment [102]. The severity of a specific event describes its intensity, *not* its outcome, and is graded on a scale that includes the designations mild, moderate and severe. Mild (or minor) adverse events include minor, irritant-type symptoms that are tolerated without affecting the usual functional activities of the patient. They do not require specific medical intervention but only the discontinuation of product use. Moderate adverse events include moderate symptoms that might cause some discomfort or interference with the usual functional activities but do not cause any concern for the patient's overall safety. They usually improve by simple therapeutic measures. Severe adverse events include severe symptoms that interrupt the patient's usual functional activities but are not life-threatening. They generally require immediate medical intervention or hospitalization [106]. It is important to note that the terms "serious" and "severe" are not synonymous and should not be used interchangeably. The term "severe" is used to describe the intensity (severity) of a specific event; the event itself, however, might be of relatively mild medical seriousness in terms of its outcome. An example of such severe but non-serious medical events is severe headache.

Adverse events can be further categorized according to the onset and expectedness of symptoms, as well as their causal relationship (causality) with the medical product. According to the onset of symptoms, adverse events are

characterized as acute (<1 h), subacute (1–24 h), or delayed (>1 day to several weeks) [107]. Depending on whether the specific adverse events were previously observed with the use of the medical product, or if their type and severity are consistent with information provided in the product's labeling information, these can be characterized as expected or unexpected [105]. Based on the degree of certainty about the causal relationship between the exposure to the medical product and the observed event, adverse events can be classified as: definitely, probably, possibly, unlikely or unrelated to the medical product [105].

Safety of pediatric contrast-enhanced ultrasound studies with intravenous administration of ultrasound contrast agents

Description of the safety studies

Many original research studies with the intravenous use of UCAs have been reported in children. These studies were conducted either with pediatric-only cohorts or with mixed adult and pediatric cohorts. To estimate the prevalence of adverse events reported in published pediatric studies, we performed a literature search in the National Library of Medicine's PubMed database to identify all original research studies that were conducted with the intravenous use of the second-generation UCAs SonoVue/Lumason, Optison or Definity in the pediatric population (age ≤18 years) and published in English. We excluded studies with mixed pediatric and adult populations if they lacked appropriate subgroup analysis by age that could allow summarization of safety data in children. We also excluded pediatric review articles from our analysis. Although they describe the pediatric population and include relevant figures, they lack total reported numbers and therefore cannot be used for calculations. For each of the pediatric-only original research CEUS studies included in our analysis, we recorded the total number of children who underwent CEUS examinations and the total number of CEUS examinations. The total number of UCA injections performed was not consistently reported in all studies so we did not include this in our analysis.

We documented the presence and type of reported adverse events, as well as the onset of symptoms in relation to the intravenous UCA administration. As of August 2021, we identified 57 studies: 12 prospective [7, 10, 24, 25, 34–36, 56–60], 22 retrospective [8, 9, 11–22, 26, 28–33, 61], 19 case reports (n<5 children) [37–55], 1 registry [5], 1 survey [6] and 2 studies of indeterminate design [23, 27]. The cumulative number of children included was 4,518 and the total number of CEUS examinations performed was 4,906.

Among the 57 studies, 51 were conducted with SonoVue/Lumason (7 prospective, 21 retrospective, 19 case reports, 1 registry, 1 survey and 2 of indeterminate design) and included a total of 4,306 children who underwent 4,533 CEUS examinations [5–55]. Of the remaining studies, 5 were conducted with Optison (all prospective) with a total of 96 children enrolled and 251 CEUS examinations performed [56–60], and 1 retrospective study was conducted in a pediatric population with the intravenous use of Definity [61]. The last study included a total of 113 children and CEUS examinations [61]. In addition, two prospective studies that used intravenous Optison included a subset of 3 children who underwent 9 CEUS examinations with Definity [56, 57].

Intravenous ultrasound contrast agent safety evaluation protocols

Different methods for performing safety evaluations during intravenous administration of UCAs have been applied and reported in the published pediatric CEUS studies. Clinical studies can be classified into five major categories according to how safety was monitored. Here we describe these categories and the number of studies and children included in each. The first category includes studies with monitoring of vital signs (e.g., heart rate, blood pressure, oxygen saturation) for detection of acute adverse events and a follow-up protocol for delayed adverse events (e.g., interview, review of medical records). These criteria were met by 12 studies that included 693 children and 878 intravenous CEUS examinations [7, 10, 12, 24, 25, 29, 35, 56–60]. The second category includes studies with clinical observations within the department for acute adverse events and review of medical records for delayed adverse events. These criteria were met by 6 studies that included 483 children and 500 intravenous CEUS examinations [8, 13, 16, 17, 20, 31]. The third category of studies included review of medical records for acute and delayed adverse events. These criteria were met by 2 studies that included 296 children and 400 intravenous CEUS studies [9, 61]. The fourth category of studies commented on the presence or absence of adverse events but without specifically defining the safety methodology applied. These criteria were met by 12 studies that included 2,885 children and 2,912 intravenous CEUS studies [5, 6, 14, 15, 18, 19, 23, 26, 27, 32, 33, 54]. Finally, the fifth category of studies did not comment on the presence or absence of adverse events. These criteria were met by 25 studies that included 161 children and 216 intravenous CEUS exams [11, 21, 22, 28, 30, 34, 36–53, 55].

As mentioned, 12 studies included comprehensive safety evaluations with monitoring of vital signs. Eleven of these 12 studies presented a comprehensive protocol describing how safety evaluations were performed and 1 study reported

that monitoring was performed in an intensive care unit. Seven of these studies were performed with the use of SonoVue/Lumason [7, 10, 12, 24, 25, 29, 35] and 5 with Optison [56–60]. The largest prospective pediatric study focusing exclusively on the safety of SonoVue came from China and comprised 312 pediatric patients who in total received 600 intravenous injections of SonoVue, including children under anesthesia or sedation [7]. Safety evaluations included vital signs monitoring during or shortly after CEUS scan and follow-up evaluations. Vital signs (heart rate, respiratory rate, oxygen saturation and blood pressure) were recorded at three distinct time intervals: before UCA administration, immediately after UCA administration, and 15 min later. The follow-up observations also included vital sign monitoring and were performed 24 h and 72 h after CEUS. The second largest prospective pediatric safety study came from Poland and included 137 children who underwent 161 CEUS examinations with intravenous SonoVue [10]. This study described a detailed plan for monitoring adverse events, including completion of a safety questionnaire by a parent/guardian 1 day before the scheduled examination. The questionnaire provided information on sensitivity to drugs and blood products, high blood pressure episodes, heart surgery and pregnancy status (in older girls). During CEUS exams, vital signs (blood pressure, heart rate, oxygen saturation and electrocardiogram) were monitored and recorded for the duration of the examination and 30 min after its completion. In addition, a follow-up US scan was performed 30 min after UCA administration to determine the presence of residual UCA microbubbles in previously examined regions or large vessels (aorta, inferior vena cava, pulmonary vein). Four other smaller pediatric studies with intravenous administration of SonoVue included detailed protocols for safety evaluations; two of these studies came from Italy and two from the United States [12, 24, 29, 35]. One included recording of vital signs (blood pressure, heart and respiratory rates, and percentage of oxygen saturation in the blood) and biochemical liver and kidney laboratory tests (transaminase and creatinine levels) [24]. In another study the same vital signs were recorded for 24 h as well as liver and kidney laboratory tests [12]. The third study included recording of the vital signs (heart rate, blood pressure and oxygen saturation) before UCA injection and during a 30 min post-injection observation period, as well as a telephone interview 24 h and 1 week after examination [35]. The fourth study performed with the intravenous use of SonoVue exclusively included neonates and infants. Although it did not describe a detailed monitoring plan, it did mention that close monitoring after the examinations was performed in the intensive care unit [29]. Recently, a study was conducted in the United States comprising a small cohort of neonates in the intensive care unit who underwent intravenous CEUS with Lumason, including neonates with congenital heart disease and/or a right-to-left vascular shunt [25]. In this study, neonates were observed for evidence of hypersensitivity reactions. In addition, vital signs (oxygen saturation, respiratory rate and continuous cardiac rate and rhythm) were monitored prior to, during and for 30 min following the CEUS examination, using pulse oximeter and cutaneous leads [25].

Similar comprehensive safety monitoring plans were reported in three studies with the intravenous use of Optison, all performed at the same institution in the United States [56, 57, 59]. Two of these studies were conducted under FDA approval of an Investigational New Drug Application (IND) [57, 59]. In these studies, the children underwent continuous electrocardiogram (ECG) monitoring during CEUS. Within 5 min after the injection, an ECG rhythm strip was printed and later interpreted by a cardiologist, and a 12-lead ECG was performed within 4 h after CEUS. Oxygen saturation was continuously monitored by pulse oximetry during UCA injection and for 30 min after CEUS. Blood pressure and heart and respiratory rates were recorded 1 min and 5 min after UCA injection and 30 min after CEUS exam. The children/guardians were interviewed immediately after each CEUS examination and again 24–48 h later to identify any immediate or delayed adverse effects that could be attributed to the UCA. Focused neurologic examination was performed within 30 min to 2 h after CEUS. The heart and lungs were auscultated 30 min after CEUS. In some children, fundoscopy was performed before and within 24 h after CEUS [56, 59].

Implementation of a comprehensive methodology for safety data collection in clinical studies is essential to accurately assess and adequately characterize the risks of any medical product, including UCAs. This was particularly important during the early stages of CEUS applications in children in order to determine that it could be used safely. However, following FDA pediatric approvals, a selective approach for safety data collection might be adequate and appropriate [108]. The FDA acknowledges the rationale for more selective post-approval safety surveillance when the drug's safety profile is established to the extent that it is reasonable to conclude that the occurrence of common, non-serious adverse events in the population to be studied will be similar to rates observed in previously conducted clinical investigations [108]. This approach aims to maintain a balance between collecting data that will not be useful and collecting sufficient data to allow adequate characterization of the safety profile of a drug without compromising the welfare of study participants and the integrity and validity of safety data [108].

Adverse events with intravenous administration of ultrasound contrast agents

Serious adverse events

A total of 57 studies reported 4,906 intravenous CEUS examinations in 4,518 children. Serious adverse events were reported in 10 children who received intravenous SonoVue/Lumason: 5 were anaphylactic or severe hypersensitivity reactions [5, 6, 10]; 3 were acute episodes of hypotension (with or without any other symptoms) [7]; 1 was an episode of severe arterial hypotension, flushing and emesis that was not further characterized by the authors (we concluded that this was an anaphylactic/hypersensitivity reaction based on the symptoms) [13]; and 1 was an indeterminate severe adverse reaction (personal communication within a study, but the authors did not provide any further information) [17]. No serious adverse events in children were reported in 96 and 116 children who underwent intravenous CEUS with Optison and Definity, respectively.

Tables 1, 2 and 3 [5–61] present the original research CEUS studies that were performed with the intravenous administration of SonoVue/Lumason, Optison and Definity in pediatric-only cohorts up to August 2021. For each referenced study, we report the total number of CEUS exams performed per child, the total number of children who underwent intravenous CEUS exams and the number of children who experienced adverse events.

The fact that most of these reactions were anaphylactic or severe hypersensitivity reactions warrants a brief discussion of hypersensitivity and anaphylaxis before reviewing descriptions of specific events in the CEUS studies.

"Hypersensitivity" is a broad term that is defined as objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus at a dose tolerated by normal subjects and may be caused by immunologic (allergic) and non-immunologic mechanisms [109]. The original Gell and Coombs classification categorizes hypersensitivity reactions into four subtypes (I–IV) according to the type of immune response and the effector mechanism responsible for cell and tissue injury: type I, immunoglobulin E (IgE) mediated; type II, cytotoxic or immunoglobulin G/immunoglobulin M (IgG/IgM) mediated; type III, IgG/IgM immune complex mediated; and type IV, delayed-type hypersensitivity or T cell mediated. The first three types are considered immediate-onset hypersensitivity reactions because they occur within 24 h, and the fourth type is considered a late-onset hypersensitivity reaction. The most serious form of immediate-onset hypersensitivity reaction is anaphylaxis. "Anaphylaxis," or anaphylactic reaction, is a medical emergency and is defined as a serious and potentially life-threatening systemic or hypersensitivity reaction with sudden onset of symptoms and signs after exposure to a provoking agent; it can affect multiple organ systems. Its signs and symptoms can occur alone or in combination, within minutes or up to several hours after exposure to an agent. It is important to note that according to the definition from the World Allergy Organization, the correct term, "anaphylaxis," is preferred to terms such as allergic reaction, acute allergic reaction, systemic allergic reaction, acute IgE-mediated reaction, anaphylactoid reaction or pseudo-anaphylaxis [110]. The characteristic signs and symptoms of anaphylaxis are described next [111]. Pediatric radiologists, sonographers and medical staff who participate in CEUS examinations should be able to promptly recognize these symptoms and to perform specific actions for their management:

a) skin, subcutaneous, and mucosal tissues (e.g., generalized rash, flushing, itching, urticarial [hives], angioedema, swelling of lips, tongue, palate);
b) respiratory (e.g., congestion, rhinorrhea, sneezing, dry cough, hoarseness, wheeze, chest tightness, bronchospasm, stridor, dyspnea, reduced peak expiratory flow rate, hypoxemia);
c) cardiovascular (e.g., tachycardia, bradycardia [less common], other arrhythmias, hypotension, hypotonia [collapse], dizziness, feeling faint, incontinence, cardiac arrest);
d) central nervous system (e.g., uneasiness in infants and children, sudden behavioral change, altered mental status, dizziness, confusion, headache); and
e) gastrointestinal (e.g., metallic taste, stomach cramping, vomiting, diarrhea).

Low systolic blood pressure for children is defined as less than 70 mmHg in children ages 1 month to 1 year, less than 70 mmHg + (2 × age) in children age 1–10 years, and less than 90 mmHg in those 11–17 years. Normal heart rate ranges 80–140 beats per minute (bpm) at ages 1–2 years, 80–120 bpm at age 3 years, and 70–115 bpm after age 3 years. Infants are more likely to have respiratory compromise than hypotension or shock, and in this age group shock is more likely to manifest initially by tachycardia than by hypotension [111].

Details of reported serious adverse events with intravenous use of ultrasound contrast agents

In the 2012 European survey, questionnaires related to pediatric CEUS use were distributed to potential users of CEUS in Europe [6]. A total of 948 intravenous CEUS examinations were performed in 30 different centers. The analyzed data of the survey did not report any serious adverse events from the intravenous use of UCAs. However, one severe anaphylactic reaction was reported in datasets that were incomplete or mixed with adult applications. This adverse event

Table 1 Pediatric-only original research contrast-enhanced ultrasound (CEUS) studies conducted with the intravenous administration of SonoVue/Lumason

First author, year, [ref]	CEUS exams (*n*)	Children (*n*)	Children with adverse events (*n*)	
			Serious	Non-serious
Dietrich, 2021, [5][a,b]	1,676	1,676	4	15
Riccabona, 2012, [6][c,d]	948	948	0	5
Mao, 2019, [7]	312[e]	312	3[f]	3[g]
Yusuf, 2017, [8]	305	305	0	2
Torres, 2017, [9]	287	183	0	0[h]
Piskunowicz, 2015, [10]	161[i]	137	1	0
Torres, 2018, [11]	74	34	0	0
Menichini, 2015, [12]	73	73	0	0
Knieling, 2016, [13]	69[j]	54	1	2[k,l]
Di Renzo, 2020, [14]	69[m]	46	0	0
Pschierer, 2015, [15]	56	56	0	0
Jacob, 2013, [16]	44	44	0	0
Stenzel, 2013, [17]	39	37	0[n]	1
Torres, 2021, [18][o]	36	36	0	0
Karmazyn, 2021 [19]	33	29	0	0
Jung, 2020, [20]	33	33	0	0
Durkin, 2015, [21][p]	31	31	0	0
Fang, 2018, [22]	30	30	0	0
Bonini, 2007, [23]	30	30	0	0
Valentino, 2008, [24]	27	27	0	0
Squires, 2021, [25]	26	26	0	0
Ponorac, 2021, [26][q]	24	24	0	1
Mudambi, 2019, [27]	20	20	0	0
Back, 2019, [28]	20	17	0	0
Kastler, 2014, [29][r]	12	12	0	0
Bowen, 2020, [30][s]	12	7	0	0
El-Ali, 2020, [31]	10	10	0	0
Deganello, 2017, [32]	10	10	0	0
Kapur, 2015, [33]	9	9	0	0
Hwang, 2019, [34]	8	8	0	0
Hains, 2017, [35]	7	7	0	1
Sridharan, 2021, [36]	6	6	0	0
Chan, 2021, [37]	5	5	0	0
Svensson, 2008, [38][t]	5	1	0	0
Rafailidis, 2017, [39][u]	4	3	0	0
Oldenburg, 2004, [40][v]	3	2	0	0
Glutig, 2021, [41]	2	2	0	0
Thimm, 2019 [42]	2	2[w]	0	0
Hwang, 2018, [43]	2	2	0	0
Luo, 2009, [44][x]	2	1	0	0
Kljucevsek, 2021, [45]	1	1	0	0
Sekej, 2020, [46]	1	1	0	0
Trinci, 2019, [47]	1	1	0	0
Lorenz, 2019, [48]	1	1	0	0
Hwang, 2018, [49]	1	1	0	0
Piorkowska, 2018, [50]	1	1	0	0
Aguirre Pascual, 2017, [51]	1	1	0	0
Al Bunni, 2014, [52]	1	1	0	0
Yusuf, 2013, [53]	1	1	0	0
Mandry, 2007, [54]	1	1	0	0
Valentino, 2006, [55]	1	1	0	0
Total: 51 studies[y]	4,533	4,306	9	30

[a]The design of this study suggests that there might be possible overlap in the number of children included here and the number of children reported by the same contributing groups/institutions in their original research studies as well as in other studies with similar design included in this table (e.g., the previously published European pediatric CEUS survey) [6]

[b]The authors included 19 children who experienced adverse reactions. Of these 19 children, the authors stated that 3 children developed symptoms that were unlikely to be attributable to the ultrasound contrast agent (UCA) administration, 1 child developed symptoms that were considered a nocebo effect and 15 children had hypersensitivity reactions: 6 mild, 5 moderate and 4 severe. Here we included 19 children with adverse reactions. The authors characterize the adverse reactions based on their severity, but not according to their seriousness. For the purpose of this analysis, we concluded that the 4 severe hypersensitivity reactions were serious and the remaining 15 adverse reactions were non-serious

Table 1 (continued)

[c]The design of this study suggests that there might be possible overlap in the number of children included here and the number of children reported by the same contributing groups/institutions in their original research studies as well as in other studies with similar design included in this table (e.g., the subsequently published European Federation of Societies for Ultrasound in Medicine and Biology pediatric CEUS registry) [5]

[d]In the results section, the author mentioned two adverse events, one severe anaphylactic reaction and one urticaria, reported in two adolescents who were included in datasets that were incomplete or mixed with an adult population. These datasets were not used for further analysis in the survey. Here we did not include these two additionally reported adverse events because they were not included in the survey analysis. However, for the purpose of our safety summary review (see text), we counted these two additional adverse events (one presumably serious and the other presumably non-serious) in the calculation of the overall adverse events rates

[e]The study included 312 children who underwent a total of 600 intravenous injections of SonoVue. We understand that several children underwent repeated injections of SonoVue in the same CEUS exam. For the purpose of this analysis, we deduced that 312 CEUS exams were performed

[f]The seriousness of these three adverse events was not characterized by the authors. However, the authors stated that anti-shock therapy was administered for management in three cases. Therefore, we deduced that these were serious adverse events

[g]In the discussion section, three adverse events were specifically reported as minor. Here we included them as non-serious adverse events

[h]One patient experienced itching the day after intravenous UCA administration. The authors stated that this was a reaction to a concomitantly administered drug. Therefore, this was not counted by the authors as an adverse event from the UCA

[i]There was a discrepancy in the total number of CEUS exams reported in the abstract (n=167) and the results section (n=161). The numbers provided in the results section are presented here

[j]The study included 40 children who underwent 55 CEUS exams. There is an addendum at the end of this publication in which 14 additional CEUS applications were reported. It is not specified whether 14 was the number of CEUS examinations, intravenous injections or children enrolled. Here we included them as 14 additional CEUS examinations in 14 additional children

[k]One case of severe adverse reaction following UCA administration is included in an addendum at the end of this publication. We included this case in our analysis

[l]The authors stated that one child was admitted to the intensive care unit after a CEUS exam. The child was diagnosed with dissociative disorder. The authors stated that there was no causal relationship of this reaction to the application of the UCA. The authors did not count this as an adverse event from the UCA. Therefore, we did not include this as an adverse event in our safety analysis

[m]The study included 46 children. The authors stated that 4 CEUS examinations were performed at admission and a total of 65 CEUS examinations were performed at follow-up. Here we included 46 children and 69 CEUS examinations

[n]In this study, no severe adverse events were reported. However, the author quoted information from personal communication regarding two cases of severe adverse events. The location of the first case (Gdansk, Poland) seems to match with a patient who was published in a dedicated study already included in this table. The location of the second case (Halle [Saale], Germany) does not seem to match with any previously published case. Here we did not include these two severe adverse events that were not reported in the study itself. However, the unpublished case from Germany was included in the calculation of the overall adverse events rates reported in our safety review. The published case from Poland was only counted once in our safety analysis

[o]The authors mentioned that 287 CEUS exams were performed during the study period, but 36 CEUS exams were eligible for analysis. Here we included 36 children and 36 CEUS exams

[p]The total number of children who had CEUS examinations and the total number of CEUS examinations performed during the study period were not clearly stated by the authors. We understand that the study analyzed 31 children who underwent intravenous CEUS. Here we included 31 children and deduced that these children underwent 31 CEUS exams

[q]The authors mentioned that 46 children had CEUS exams, but 24 children were eligible for analysis. Here we included 24 children and 24 CEUS examinations

[r]The authors mentioned that 16 infants underwent a total of 20 consecutive transfontanelle CEUS examinations. Of those 16 infants, 12 were considered evaluable for analysis. Here we included 12 infants and 12 CEUS examinations

[s]The study included 7 children. The authors stated that 5/7 children had a follow-up CEUS exam. Here we included 12 CEUS examinations in 7 children

[t]The study included 1 child. The authors stated that CEUS examination was repeated on days 1, 3 and 7 postoperatively, as well as after 1 month and 3 months. Here, we included 5 CEUS examinations in 1 child

[u]The study included 3 children. The authors stated that 1/3 children had a follow-up CEUS exam. Here we included 4 CEUS examinations in 3 children

[v]The study included 2 children. Each child had an initial CEUS examination. One child had an additional follow-up CEUS examination. Here we included 3 CEUS examinations in 2 children

[w]The study included 2 children (<18 years) and 1 young adult (20 years old). Here we included the 2 pediatric patients

[x]The study included 1 child. One CEUS examination was performed initially. A follow-up CEUS examination was also performed after 3 months. Here we included 2 intravenous CEUS examinations in 1 child

[y]For each referenced study, the total number of CEUS exams that were performed per child and the total number of children who underwent intravenous CEUS exams is reported. If the authors of a referenced study did not clearly state the total number of CEUS exams performed, for the purpose of this analysis, we deduced that each child had one CEUS exam. The total number of SonoVue/Lumason injections that were performed during each CEUS exam was not consistently reported in all studies and therefore is not included in this table. Studies are presented in descending order from the highest number of CEUS examinations performed to the lowest, with respective references [ref]. The number of children who experienced adverse events (serious and non-serious) is reported for each referenced study

Table 2 Pediatric-only original research contrast-enhanced ultrasound (CEUS) studies conducted with the intravenous administration of Optison

First author, year, [ref]	CEUS exams (*n*)	Children (*n*)	Children with adverse events (*n*)	
			Serious	Non-serious
Coleman, 2014, [56][a,b]	126	32	0	3
McCarville, 2016, [57][a,c]	74	13	0	1
McMahon, 2005, [58]	20	20	0	4
McCarville, 2012, [59][a]	13[d]	13	0	2[e]
Armstrong, 2017, [60]	18	18	0	0
Total: 5 studies[f]	251	96	0	10

[a]These three studies were conducted by the same group/institution. The design of these studies suggests that there might be possible overlap in the number of children included here

[b]In this study 34 children underwent a total of 134 CEUS examinations. Of the 34 children, 32 children received Optison and underwent a total of 126 CEUS exams and 2 children received Definity and underwent a total of 8 CEUS exams. In this table we present only the results from the Optison use. The results from Definity use are presented in Table 3

[c]In this study 25 children underwent CEUS with the intravenous use of Optison, but only 13 were considered evaluable for analysis. These 13 children underwent a total of 74 CEUS examinations. Here we included 13 children and 74 CEUS exams

[d]In this study 13 children underwent 28 intravenous injections of ultrasound contrast agent. The total number of CEUS examinations was not clearly stated by the authors. Here we included 13 children and 13 CEUS exams

[e]In this study, there was one case of hyperactivity/irritability, but the authors stated that the association of this symptom with the ultrasound contrast agent was not clear. The authors did not consider this symptom an adverse event. We did not include this as an adverse event in our analysis

[f]For each referenced study, the total number of CEUS exams that were performed per child and the total number of children who underwent intravenous CEUS exams is reported. If the authors of a referenced study did not clearly state the total number of CEUS exams performed, for the purpose of this analysis, we deduced that each child had one CEUS exam. The total number of Optison injections that were performed in each CEUS exam was not consistently reported in all studies and therefore is not included in this table. Studies are presented in descending order from the highest number of CEUS examinations performed to the lowest, with respective references [ref]. The number of children who developed adverse events (serious and non-serious) is reported for each referenced study

occurred in an adolescent girl with an oncological condition and multiple known allergies and required resuscitation. This adverse event was not used for further analysis by the authors of the survey and therefore is not included in Table 1 of the safety analysis summary reported here. However, we included this case in the calculation of the overall adverse event rates.

Table 3 Pediatric-only original research contrast-enhanced ultrasound (CEUS) studies and cohorts conducted with the intravenous administration of Definity

First author, year, [ref]	CEUS exams (*n*)	Children (*n*)	Children with adverse events (*n*)	
			Serious	Non-serious
Kutty, 2016, [61]	113	113	0	13
Coleman, 2014, [56][a,b]	8	2	0	0
McCarville, 2016, [57][a,c]	1	1	0	0
Total of study subsets[d]	122	116	0	13

[a]These two study subsets were conducted by the same group/institution. The design of these studies suggests that there might be possible overlap in the number of children included here

[b]In this study, 2 children underwent 8 CEUS exams with the intravenous use of Definity. All other children underwent CEUS with the intravenous use of Optison and are included in Table 2

[c]In this study, 1 child underwent CEUS with the intravenous use of Definity. All other children underwent CEUS with the intravenous use of Optison and are included in Table 2

[d]For each referenced study, the total number of CEUS exams that were performed per child and the total number of children who underwent intravenous CEUS exams is reported. If the authors of a referenced study did not clearly state the total number of CEUS exams performed, for the purpose of this analysis, we deduced that each child had one CEUS exam. The total number of Definity injections that were performed in each CEUS exam was not consistently reported in all studies and therefore is not included in this table. Studies are presented in descending order from the highest number of CEUS examinations performed to the lowest, with respective references [ref]. The number of children who developed adverse events (serious and non-serious) is reported for each referenced study

Three presumably serious adverse events were reported from the largest single-center prospective study in China, which included a total of 312 children who underwent 600 intravenous injections of SonoVue [7]. All three children had hypotension — one as an isolated symptom, one associated with cough and one in combination with rash/tachycardia. While the authors did not specify the severity of these three adverse events, they stated that these adverse events required anti-shock therapy. Therefore, in our analysis we deemed them serious adverse events. The details of these three adverse events are as follows: a 13.3-year-old boy developed a rash on the face, chest and abdomen, tachycardia (148 bpm) and hypotension (66/34 mmHg); a 6.3-year-old boy developed continuous cough and hypotension (53/17 mmHg); and a 3-year-old girl had hypotension (78/47 mmHg). These events occurred immediately after contrast administration and we therefore considered them acute. The first child required administration of

dexamethasone, methylprednisolone, calcium gluconate and adrenaline, whereas the latter two received methylprednisolone. In all three cases, symptoms completely resolved.

One case of anaphylaxis was described in a large prospective study from Gdansk, Poland, that evaluated the safety of SonoVue in children [10]. This was the case of an 11-year-old girl with metastatic gastrointestinal stromal tumor of the stomach wall who experienced severe, potentially life-threatening anaphylactic shock. Forty-three seconds after intravenous administration of SonoVue, the girl developed generalized pruritus, nausea, hypotension (systolic blood pressure <70 mmHg) and tachycardia (up to 200 bpm). One minute later, she experienced bradycardia (up to 45 bpm) and desaturation (O_2<60%). CEUS examination was immediately discontinued and treatment was initiated with intravenous epinephrine, fluids (0.9% sodium chloride) and oxygen. All symptoms resolved 2 h later.

Another case of a severe adverse reaction was included as an addendum at the end of a study from Erlangen, Germany [13]. This occurred in another 11-year-old girl who received intravenous administration of SonoVue. The girl developed arterial hypotension, flush and emesis and required short-term inpatient monitoring and treatment with steroids, antihistamines and fluids.

Two cases of severe adverse reaction were quoted in a study as part of the author's personal communication with authors from other institutions [17]. The study itself presented the single-center experience from SonoVue use in children. No serious adverse events occurred at this specific center. However, the author discussed two cases of severe adverse events that occurred at two European centers other than the author's own institution. The first case, from Halle (Saale), Germany, does not seem to have been previously published and therefore is included in our safety analysis. In the second case of severe anaphylactic reaction, the location identifier seems to match with the case from Gdansk, Poland, that was previously published and already included in our safety review. In both of these cases, no further descriptive information regarding the type, presentation or management of adverse events was provided by the author.

The pediatric registry of EFSUMB reported 4 severe hypersensitivity reactions out of 1,676 children who underwent intravenous CEUS with SonoVue [5]. All reactions were acute and occurred within the first 3 min (ranging 43–180 s) following intravenous administration of SonoVue. Although the authors did not explicitly comment on the seriousness of the adverse events, given the detailed description of the symptoms and subsequent management we deduced that these four severe adverse events were also serious. Specifically, an 11-year-old girl developed symptoms of pruritus, nausea, hypotension, tachycardia/bradycardia, decreased oxygen saturation (60%) and loss of consciousness. Her symptoms resolved following intravenous administration of epinephrine, oxygen and crystalloid fluid bolus. In this case, the child's demographics, presenting symptoms and management seem to match with those described in the case from Gdansk, Poland. This child is thought to be described in three different CEUS studies that were included in our analysis; however, we only counted her one time [5, 10, 17]. The second severe hypersensitivity reaction in the EFSUMB registry occurred in a 4-year-old boy who developed widespread urticaria and cardiovascular collapse with loss of consciousness. He required adrenaline, chlorpheniramine, hydrocortisone, crystalloid fluid bolus and oxygen followed by intubation. A third case was in a 16-year-old boy who developed symptoms 3 min after SonoVue administration, including pain in the left upper quadrant, cold sweat, decreased oxygen saturation (89%) and inability to communicate but without loss of consciousness. His symptoms resolved following administration of crystalloid fluid, cortisone, oxygen, lorazepam and piritramide. The fourth case was in an 11-year-old girl who experienced a burning sensation of the airways, redness (the area of redness was not specified by the authors), nausea, vomiting, bradycardia/tachycardia, hypotension and decreased oxygen saturation (90%). Symptoms resolved with crystalloid fluid and intravenous administration of prednisolone and dimetindene [5].

With the caveats described here, in the published pediatric-only CEUS studies included in our analysis, the overall incidence rate of serious adverse events is 0.22% (10/4,518) of children and 0.20% (10/4,906) of all CEUS examinations.

We highlighted the children with severe adverse events who appear to have been included in the analysis of more than one publication. We also acknowledge that there is possible duplication in the number of children/CEUS exams reported in studies that were conducted by the same groups/institutions, as well as possible overlap in the number of children/CEUS exams that were reported in the two cumulative safety reviews (European CEUS survey and EFSUMB registry) and in the original published reports.

It is also important to note that from these published data we calculated the incidence of adverse events based on the total number of evaluable children and CEUS examinations performed per child. Several studies enrolled larger cohorts of children who underwent CEUS examinations, but not all of them were considered eligible for analysis by the authors of these studies and therefore were subsequently excluded from those studies' populations. In addition, several studies reported that UCA injections were repeated during a single CEUS examination and therefore the actual number of UCA injections is expected to be larger than the reported number of children and CEUS examinations. Thus, the incidence of adverse events per number of injections is expected to be lower than what we reported.

Details of reported non-serious adverse events with intravenous use of ultrasound contrast agents

A total of 54 children reportedly had 76 non-serious adverse events following intravenous CEUS: 31 children with 47 events following SonoVue/Lumason [5–8, 13, 17, 26, 35]; 10 children with 14 events following Optison [56–59]; and 13 children with 15 events following Definity [61].

The 47 non-serious adverse events that were reported with SonoVue/Lumason were: skin reactions (n=15) (3 rash, 2 focal or multifocal areas of skin redness, 2 flushed face, 2 urticarial rash, 2 indeterminate skin reaction, 1 generalized skin flush, 1 single wheal, 1 erythema, 1 livid skin spots); taste alteration (n=4) (3 strange taste, 1 strong metallic taste); nausea (n=3); abdominal/stomach pain (n=3); tachycardia (n=2); hypotension (n=2); hyperventilation before or after the injection (n=2); stupor-like reaction (n=2); shortness of breath (n=1); dizziness (n=1); chest pain (n=1); fatigue (n=1); headache (n=1); hypertension (n=1); vomiting (n=1); chills (n=1); conjunctival injection (n=1); and cough (n=1) [5–8, 10, 13, 17, 26, 35]. Here we included an adverse event (urticaria) in an adolescent that was included in the European pediatric CEUS survey, despite not being part of this study's analyzed population [6]. The seriousness of this event was not specified, and therefore is indeterminate, though we assume that it was a non-serious adverse event. Of these 47 events, four were subacute: one case of headache was described 1 h after an intravenous CEUS study [35], one case of transient tachycardia with mild hypotension 4 h later, and one case of transient hypertension 1 h after the end of a CEUS examination [35]. All other adverse events appeared during or immediately after the intravenous injection and resolved by themselves without any medication required.

The 14 non-serious adverse events reported with Optison in 10 children included brief taste alteration (n=7), transient headache (n=3), mild transient tinnitus (n=2) and lightheadedness (n=2) [56–59]. All these events were acute.

The 15 non-serious adverse events that were reported with Definity in 13 children included chest pain (n=7), fatigue (n=3), back pain (n=1), neck pain (n=1), dizziness (n=1), headache (n=1) and shortness of breath (n=1) [61]. All of these were acute and occurred during the scan.

The overall incidence rate of non-serious adverse events in the published studies was 1.20% (54/4,518) of children and 1.10% (54/4,906) of CEUS examinations, including the 1 additional case of urticaria that was stated within the European survey [6].

Tables 4, 5 and 6 present all adverse events reported in pediatric-only original research CEUS studies with the intravenous use of SonoVue/Lumason, Optison and Definity, respectively, stratified by seriousness, acuity and frequency of incidence [5, 6, 10, 13, 17, 57].

Safety of pediatric contrast-enhanced voiding urosonography studies with intravesical administration of ultrasound contrast agents

Intravesical ultrasound contrast agent safety evaluation protocols

We performed a literature search in the National Library of Medicine's PubMed database to identify all original research studies that were conducted with the intravesical use of the second-generation UCAs SonoVue/Lumason, Optison and Definity in the pediatric population (ages ≤18 years) and published in English. We excluded studies with mixed pediatric and adult populations if they lacked appropriate subgroup analysis by age that could allow summarization of safety data in children. For each study included in our analysis, we recorded the total number of children who underwent contrast-enhanced voiding urosonography (ceVUS) examinations and the adverse events reported in these studies.

As of August 2021, 31 studies examined the intravesical use of second-generation UCAs in children, including a total of 12,362 children. Of these, 28 studies were carried out with SonoVue/Lumason encompassing 12,327 children [6, 62–85, 87, 88, 90]; the remaining 3 studies used Optison in a total of 35 children [86, 89, 91]. There were no reported studies with the intravesical use of Definity.

Of these studies, two included comprehensive safety evaluation protocols aiming to detect the adverse events related to the intravesical use of UCAs [63, 86]. The first study was conducted with SonoVue [63]. A total of 1,010 children were observed during ceVUS for signs of localized or generalized anaphylactic reaction (perineal skin or mucosal tissue reaction, any pathological discharge from the urethra, vagina or rectum). In addition, vital signs were measured by a dedicated physician assistant during the examination, including pulse rate by palpation of the radial artery and respiratory rate by counting breath frequency. Measurements were repeated every 15 min for 1 h after completion of the study. Body temperature was also measured at the end of the examination and 1 h later. One week after the ceVUS examination, the same pediatric radiologist who performed the ceVUS examinations contacted all parents/guardians by phone to ask about the presence of any delayed adverse events. Urinalysis and culture test were performed in any child reported to have any adverse event.

The second study was performed with the intravesical use of Optison and was conducted under FDA approval of an Investigational New Drug Application (IND) [86]. Safety assessments were performed at baseline, during and immediately after each ceVUS and fluoroscopic voiding cystourethrography (VCUG) examination, and during a follow-up

Table 4 Incidence rates of adverse events reported in children as a result of intravenous administration of SonoVue/Lumason

Incidence rate[a]		Incidence % (*n*/4,533×100) (*n*)
Acute (<1 h)		
Serious	Anaphylactic reaction/severe hypersensitivity[b]	0.15% (7)
	Hypotension with/without additional symptoms	0.07% (3)
Non-serious[c]	Skin reaction	0.33% (15)
	Taste alteration	0.09% (4)
	Nausea	0.07% (3)
	Abdominal/stomach pain	0.07% (3)
	Tachycardia	0.04% (2)
	Hypotension	0.04% (2)
	Hyperventilation	0.04% (2)
	Stupor-like reaction	0.04% (2)
	Shortness of breath	0.02% (1)
	Dizziness	0.02% (1)
	Chest pain	0.02% (1)
	Fatigue	0.02% (1)
	Headache	0.02% (1)
	Hypertension	0.02% (1)
	Vomiting	0.02% (1)
	Chills	0.02% (1)
	Conjunctival injection	0.02% (1)
	Cough	0.02% (1)
Subacute (1–24 h)		
Serious		0% (0)
Non-serious	Headache	0.02% (1)
	Hypertension	0.02% (1)
	Tachycardia	0.02% (1)
	Hypotension	0.02% (1)

[a]Incidence rates are stratified according to the onset (acute, subacute), seriousness (serious, non-serious) and type of presenting symptoms. For each adverse event, the incidence rate was calculated as a percentage in which the numerator was the total number of the respective adverse events reported in the pediatric-only contrast-enhanced ultrasound (CEUS) studies and the denominator was the total number of CEUS exams performed with SonoVue/Lumason and reported in the published pediatric-only CEUS studies included in our analysis. Incidence rates are presented in descending order from the most to the least common

[b]Here we included three cases of severe hypersensitivity reaction reported by Dietrich et al. [5], one case of anaphylactic reaction reported by Piskunowicz et al. [10], one case of severe adverse reaction reported by Knieling et al. [13], one case of severe adverse reaction reported by Riccabona [6] and one case of severe adverse reaction reported as a personal communication in the study by Stenzel [17] (please see text). The case of severe anaphylactic reaction reported by Piskunowicz et al. (Gdansk, Poland) was counted once in our safety summary analysis, despite being presumably reported in three studies that were also included in our safety review. The severe adverse event reported by Knieling et al. was not characterized by the authors but given the described symptoms of arterial hypotension, flushing and emesis, we concluded that this was a case of anaphylactic/hypersensitivity reaction. The severe adverse event reported in the study by Stenzel was described in personal communication as coming from the center Halle (Saale), Germany

[c]Here we included the symptoms observed in each of the non-serious adverse events included in our safety review. In the study by Dietrich et al. [5], the detailed description of the symptoms observed in the adverse events that we deemed non-serious (see text) is presented in the supplementary material of their publication

Table 5 Incidence rates of adverse events[a] reported in children as a result of intravenous administration of Optison

Acute (<1 h)		Incidence % (*n*/251×100) (*n*)
Serious		0% (0)
Non-serious	Taste alteration[b]	2.8% (7)
	Headache	1.2% (3)
	Tinnitus	0.8% (2)
	Lightheadedness	0.8% (2)

[a]All adverse events reported were acute in onset. Incidence rates were stratified according to the seriousness (serious, non-serious) and type of presenting symptoms. For each adverse event, the incidence rate was calculated as a percentage in which the numerator was the total number of the respective adverse events reported in the pediatric-only contrast-enhanced ultrasound (CEUS) studies and denominator was the total number of CEUS exams performed with Optison and reported in the published pediatric-only CEUS studies included in our analysis. Incidence rates are presented in descending order from the most common to the least common

[b]In the study by McCarville et al. [57], the same child developed taste alteration in three CEUS exams. Here we counted this symptom three times

Table 6 Incidence rates of adverse events[a] reported in children as a result of intravenous administration of Definity

Acute (<1 h)		Incidence % (*n*/122×100) (*n*)
Serious		0% (0)
Non-serious	Chest pain	5.7% (7)
	Fatigue	2.5% (3)
	Back pain	0.8% (1)
	Neck pain	0.8% (1)
	Dizziness	0.8% (1)
	Headache	0.8% (1)
	Shortness of breath	0.8% (1)

[a]All adverse events reported were acute in onset. Incidence rates are stratified according to the seriousness (serious, non-serious) and type of presenting symptoms. For each adverse event, the incidence rate was calculated as a percentage in which the numerator was the total number of the respective adverse events reported in the pediatric-only contrast-enhanced ultrasound (CEUS) studies and denominator was the total number of CEUS exams performed with Definity and reported in the published pediatric-only CEUS studies included in our analysis. Incidence rates are presented in descending order from the most to the least common

telephone interview with the parents/guardians. Assessments included evaluation of body systems for signs of localized or generalized anaphylactic reactions, monitoring of heart rate and pulse oxygen saturation, and telephone questionnaire-based interview of parents/guardians and children 48 h after the examinations to evaluate for delayed adverse events. The remaining studies in this group of intravesical UCA publications did not describe a specific safety evaluation protocol for adverse events monitoring; however, the majority of them did comment on the presence or absence of adverse events.

Adverse events with intravesical administration of ultrasound contrast agents

Among the 12,362 children who underwent ceVUS examination, there were no cases of serious adverse events from the intravesical use of SonoVue/Lumason or Optison. A total of 38 non-serious adverse events were reported in two studies, i.e. 0.31% (38/12,362) of the total population [63, 86]. These non-serious adverse events were: dysuria (*n*=27), urinary retention (*n*=2), non-specific transient abdominal pain/discomfort (*n*=2), anxiety during micturition (*n*=1), crying during micturition (*n*=1), blood and mucous discharge (*n*=1), increased frequency of micturition (*n*=1), vomiting (*n*=1), perineal irritation and discomfort (*n*=1) and urinary infection (*n*=1). All symptoms were subacute in onset, self-limited and required no further consultation or hospitalization. The authors of these studies concluded that the adverse events were likely caused by the discomfort of the minimally invasive procedure of bladder catheterization itself as well as its psychological impact on the children, rather than the contrast agent used. This was thought to be the case because similar adverse events were previously described with voiding cystourethrography and radionuclide studies that included bladder catheterization [112]. Table 7 presents the pediatric-only original research studies performed with the intravesical use of SonoVue/Lumason and Optison [6, 62–91]. For each referenced study, we present the total number of ceVUS exams performed and the number of adverse events. Table 8 presents the types of all adverse events that have been reported in pediatric ceVUS studies with the use of the second-generation UCAs.

Safety of pediatric contrast-enhanced ultrasound for other uses of ultrasound contrast agents

In addition to the well-established intravenous and intravesical uses of UCAs in children, other applications have been increasingly reported and are mainly intracavitary (e.g., genitosonography, nephrosonography, fistulography) and intralymphatic (e.g., to assess patency of thoracic duct) or interventional uses. In total, five studies have been performed with the intracavitary (other than intravesical) and two with the intralymphatic use of UCAs, encompassing 19 children [92–98]. In these limited cumulative cohorts, no adverse events have been reported.

Table 7 Contrast-enhanced voiding urosonography (ceVUS) original research studies performed with the intravesical use of SonoVue/Lumason or Optison in a pediatric-only population

First author, year, [ref][a]	ceVUS exams	Non-serious adverse events
Cvitkovic-Roic, 2021, [62]	5,153	0
Riccabona, 2012 [6]	4,131	0
Papadopoulou, 2014, [63]	1,010	37
Papadopoulou, 2009, [64]	228	0
Duran, 2012, [65]	307	0
Kis, 2010, [66]	183	0
Woźniak, 2018, [67]	150	0
Piskunowicz, 2016, [68]	141	0
Battelino, 2016, [69]	116	0
Ključevšek, 2019, [70]	105[b]	0
Zhang, 2018, [71]	90	0
Ascenti, 2004, [72]	80	0
Simicic Majce, 2021 [73]	70	0
Woźniak, 2016, [74]	69	0
Kljucevsek, 2012, [75]	66	0
Siomou, 2020, [76]	60	0
Giordano, 2007, [77]	47[c]	0
Fernández-Ibieta, 2015, [78]	40	0
Velasquez, 2019, [79]	39	0
Marschner, 2021, [80]	38[d]	0
Benya, 2021, [81]	34	0
Kim, 2021, [82]	32	0
Kuzmanovska, 2017, [83]	31	0
Wong, 2014, [84]	31	0
Mane, 2021, [85]	30	0
Ntoulia, 2018, [86]	30	1
Faizah, 2015, [87]	27	0
Woźniak, 2014, [88]	17	0
Colleran, 2016, [91]	4	0
Babu, 2015, [90]	2	0
Colleran, 2016, [89]	1	0
Total: 31 studies	12,362	38

[a]Studies are presented in descending order from the highest number of ceVUS examinations performed to the lowest, with respective references [ref]. No serious adverse events were reported in any study. A few non-serious adverse events were reported in two studies

[b]In this study, 163 ceVUS exams were performed in 163 children. In 58 children important data were missing or were incomplete. Therefore, 105/163 children were considered evaluable. Here, we included 105 evaluable children

[c]In this study, 563 ceVUS exams were performed with the first-generation ultrasound contrast agent Levovist (Bayer Schering, Berlin, Germany) and 47 ceVUS exams were performed with SonoVue. Here we included the 47 ceVUS exams that were performed with SonoVue

[d]This study included 38 children and 7 adults. Here we included 38 children

Table 8 Incidence rates[a] of adverse events reported in children as a result of intravesical administration of Lumason/SonoVue or Optison

Subacute (1–24 h)		Incidence % (*n*/12,362×100) (*n*)
Serious		0% (0)
Non-serious	Dysuria	0.22% (27)
	Urinary retention	0.02% (2)
	Transient abdominal pain/discomfort	0.02% (2)
	Anxiety during micturition	0.01% (1)
	Crying during micturition	0.01% (1)
	Blood and mucous discharge	0.01% (1)
	Increased frequency of micturition	0.01% (1)
	Vomiting	0.01% (1)
	Perineal irritation and discomfort	0.01% (1)
	Urinary infection	0.01% (1)

[a]All adverse events reported were subacute in onset. Incidence rates are stratified according to seriousness (serious, non-serious) and type of presenting symptoms. For each adverse event, the incidence rate was calculated as a percentage in which the numerator was the total number of the respective adverse events reported in the pediatric-only contrast-enhanced voiding urosonography (ceVUS) studies and denominator was the total number of ceVUS exams performed with Lumason/SonoVue or Optison and reported in the published pediatric-only ceVUS studies included in our analysis. Incidence rates are presented in descending order from the most to the least common

Current contraindications of ultrasound contrast agents

There are very few rare situations in which the use of UCA is definitively contraindicated in adults and children. These are more likely related to the specific chemical composition of each of the UCAs and are listed in the respective package inserts.

Prior to April 2021, the package labels indicated that contraindications to the use of UCAs included hypersensitivity to active or inactive ingredients. In April 2021, the FDA requested the revision of the package labeling for Lumason and Definity to explicitly state that these UCAs are contraindicated in people with known or suspected polyethylene glycol (PEG) allergy. PEGs are a group of polyether compounds with various molecular weights that can be found as active or inactive ingredients in many medical, cosmetic, household, industrial and food products. PEGs are active ingredients in some bowel preparations and laxatives. PEGs are inactive in the shell of Lumason/SonoVue and Definity.

This recent FDA alert followed the review of safety data reported during a post-approval surveillance over a 10-year period. The agency cited 11 hypersensitivity reactions and two deaths related to the administration of UCAs in people with a reported history of PEG allergy [113, 114]. A literature review spanning 1977 to 2016 identified 37 people with

Table 9 Contraindications of the three ultrasound contrast agents currently used in children

Ultrasound contrast agent	Contraindication
SonoVue/Lumason [118]	Hypersensitivity to sulfur hexafluoride lipid microspheres or its components, such as polyethylene glycol (PEG)
Optison [119]	Known or suspected hypersensitivity to perflutren, blood, blood products or albumin
Definity [120]	Hypersensitivity to perflutren lipid microsphere or its components, such as polyethylene glycol (PEG)

immediate-type PEG hypersensitivity, where 28 (76%) met criteria for anaphylaxis [115]. A second series published in 2021 added 5 people to this total [116].

At the present time, documented allergy to PEG is rare and might depend on the amount and molecular weight of the PEG. Hypersensitivity reactions can be serious and severe and can even occur in people who have not previously received medications containing PEGs. This might be attributed to the common use of PEGs in many everyday household products. Some patients and families might be unaware of personal existing sensitivities, so known allergies should be reviewed, including allergies to bowel preparations.

In the pediatric CEUS literature, one case of severe anaphylactic reaction in a 4-year-old following intravenous administration of SonoVue was proved to be caused by the child's sensitivity to PEG, according to the reporting authors [5].

Following the label revision of Definity and Lumason, both the International Contrast Ultrasound Society (ICUS) and the American Society of Echocardiography issued statements reaffirming the safety of UCAs and noting the benefits of CEUS, the rarity of PEG allergy, and the vigilance on the part of CEUS practitioners to screen for allergies and to recognize and treat reactions if they occur, emphasizing the importance of having emergency medications readily available when contrast agents are administered [113, 117].

Table 9 presents the contraindications for each of the UCAs used in children [118–120]. The presence of cardiac shunts (right-to-left, bi-directional, transient right-to-left) was formerly a contraindication for all second-generation UCAs. The rationale for this contraindication was based on the theoretical potential that the UCA microbubbles could pass via the shunt from the venous system directly into the arterial system without filtration by the pulmonary capillary bed, increasing the risk for potential arteriolar ischemic or cerebral neurovascular events [102]. This hypothetical risk was based on limited research data from animal models and the false assumption that UCAs have similar properties to macroaggregated albumin microspheres, a radioactive nuclear imaging agent that contains a section in the package insert recommending caution if used in detecting a cardiac shunt, but it is not contraindicated. Since the time that the shunt contraindication appeared in the UCA label, an exhaustive review of the literature has demonstrated the lack of scientific basis for this contraindication, supporting the safe use of UCAs in routine practice. In 2016 the FDA removed the cardiac shunt contraindication from all UCA labels. Further information on the cardiac shunt issue can be found in another article of this supplement [121].

The United States Food and Drug Administration black box warning for ultrasound contrast agents

In 2007, the FDA mandated a black box warning on the package insert of approved UCAs in the United States. This black box warning described the possibility of serious cardiopulmonary reactions, including fatalities, following the use of the any of the UCAs. A black box warning (or boxed warning) is the strictest labeling requirement that the FDA can issue for medical products. It aims to alert the public and health care providers regarding the possibility of serious adverse reactions associated with the use of that product, including serious injury or death. While black box warnings are an important tool for informing the public and can decrease use of medical products in high-risk populations, they can also discourage the use of medical products in people who would benefit from them. The boxed warning for UCAs was issued in response to spontaneous reports of a small number of serious adverse events that occurred in adults after UCA administration in the early years of its introduction. However, the reported serious adverse events were not definitively attributed to UCAs, and some were later ascribed to underlying medical conditions or other medication. Since the issue of the black box warning, cumulative relevant scientific literature continues to show that UCAs have a very safe profile. Currently there is an ongoing citizen petition initiative from the ICUS for the removal of the boxed warnings from the UCA product labels. A more detailed discussion of this topic can be found in another article of this supplement [121].

Code cart for the performance of intravenous contrast-enhanced ultrasound examinations

Because serious adverse events such as anaphylaxis can occur, predominantly during intravenous CEUS, pediatric radiologists and US staff involved in CEUS examinations should be alert and prepared for immediate recognition and treatment. To facilitate immediate management of an emergency code, the presence of a resuscitation cart should be mandatory in or in the vicinity of the US units in which CEUS examinations are performed.

Bioeffects of ultrasound contrast agents

The focus of this review is on the clinical safety of using UCAs. However, it is important to remember that microscale bioeffects might result from the interaction between US waves and microbubbles. Bioeffects observed in research settings with small-animal models vary from destabilization of the molecular properties of cells and tissues (change in tensile strength or shape) to cellular erosion or lysis, and the formation of free radicals [122]. The most commonly described bioeffect is cavitation, which refers to the destruction of the gas bubbles within the US field. Within biological tissues, gas bodies serve as potential cavitation nuclei. In the absence of an acoustic wave or other mechanical stress, these gas bodies eventually dissolve. But under the influence of a US wave, a spectrum of events takes place, known as gas body activation phenomena [122–125]. These occur in proportion to the acoustic pressure of the transmitted US wave.

If the transmitted US wave is of low acoustic power (<100 kPa), microbubbles undergo linear volumetric oscillations with symmetrical expansion and contraction phases. Acoustic pressures within this range allow the microbubbles to remain intact and no significant bioeffects occur. As the acoustic power increases (100 kPa to 1 MPa), the microbubbles begin to oscillate in a non-linear fashion. When the acoustic pressure reaches relatively high values, a violent expansion and collapse of the gas bubbles is observed, known as inertial cavitation [125]. Inertial cavitation is associated with fluid jets, localized heating, and release of free radicals that accompanies gas body destruction and can damage nearby biological cells and structures [124].

Most in vivo research on microbubble bioeffects has been conducted in small animals such as mice or rats and has focused mostly on skeletal or cardiac muscle. This research has attempted to measure the observable microvascular damage as a result of gas body destruction within the vascular bed, including microvascular leakage, petechiae, cardiomyocyte death, inflammatory cell infiltration and premature ventricular contractions [126–130]. The major conclusions of these studies in small animals can be summarized as follows: (1) UCA type: In vivo detectable microvascular injury in small animals might occur with any gas-containing UCA. No observable differences could be identified among different UCAs [128]. (2) UCA dose: For the clinically relevant low dose of UCA in small-animal studies (approximating a standard human dose), the microvascular damage potential as expressed by petechiae and capillary leakage is proportional to the UCA dose. That means that in low doses, the number of observed petechiae increases in a linear correlation with UCA dose. However, at higher doses, the petechiae number reaches a plateau, meaning that the use of very high doses did not actually produce greater effects [126]. In addition, researchers noticed that there were different dose–related types of observable damage for the same volumes of injected UCA. This suggests that the microvascular damage potential is likely related to the actual number of contained microbubbles within the injected volume, rather than the UCA exact dose [128]. (3) Scanning method: The use of high mechanical index (MI) values (>0.8) results in rapid gas body destruction, while use of low MI values (<0.2) is related to minimal gas body destruction [122]. In vivo animal research studies demonstrated that inertial cavitation can occur if exposure conditions correspond to MI values greater than approximately 0.4, which therefore represents a theoretical threshold [131]. However, when interpreting the results from in vivo animal research studies, it must be noted that conditions in the human body are different from specialized conditions in research settings. Therefore, direct translation of the results from animal models to human body conditions is complex and remains the subject of active research.

Conclusion

This review article provides an overview of the safety regarding the applications of second-generation UCAs in pediatric practice. Overall, adverse events from the intravenous use of UCAs are rare. Among them, minor adverse events are reported more frequently, though serious adverse events also occur very rarely and present as anaphylactic reactions. Pediatric radiologists and medical personnel who perform CEUS exams should be aware of the signs and symptoms of these adverse events and be prepared to manage them. The presence of a resuscitation cart should be mandatory in or near US units that perform CEUS studies. Regarding the intravesical use of UCAs, a few minor adverse events have been reported, which are attributed to the bladder catheterization process. Other uses of UCAs in children are intracavitary (other than bladder), intravenous

and intralymphatic applications. Although a small number of children have been evaluated with these applications, no adverse events have been reported. Overall, the use of UCAs in children is considered to be very well tolerated. The high safety profile combined with all the added advantages of CEUS is a driver for the wider application of UCAs in pediatric US.

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Declarations

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