Published in final edited form as:

*Pediatr Crit Care Med*. 2015 February ; 16(2): 175–183. doi:10.1097/PCC.0000000000000306.

# Risk factors associated with iatrogenic opioid and benzodiazepine withdrawal in critically ill pediatric patients: A systematic review and conceptual model

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## Abstract

**Objective—**Analgesia and sedation are common therapies in pediatric critical care, and rapid titration of these medications is associated with iatrogenic withdrawal syndrome (IWS). We performed a systematic review of the literature to identify all common and salient risk factors associated with IWS and build a conceptual model of IWS risk in critically ill pediatric patients.

**Data sources—**Multiple databases, including PubMed/Medline, EMBASE, CINAHL, and the Cochrane Central Registry of Clinical Trials were searched using relevant terms from January 1, 1980 to August 1, 2014.

**Study selection—**Articles were included if they were published in English and discussed IWS following either opioid or benzodiazepine therapy in children in acute or intensive care settings. Articles were excluded if subjects were neonates born to opioid- or benzodiazepine-dependent mothers, children diagnosed as substance abusers, or subjects with cancer-related pain; if data about opioid or benzodiazepine treatment were not specified; or if primary data were not reported.

**Data extraction and synthesis—**In total 1395 papers were evaluated, 33 of which met the inclusion criteria. To facilitate analysis, all opioid and/or benzodiazepine doses were converted to morphine or midazolam equivalents, respectively. A table of evidence was developed for qualitative analysis of common themes, providing a framework for the construction of a conceptual model. The strongest risk factors associated with IWS include duration of therapy and cumulative dose. Additionally, evidence exists linking patient, process and system factors in the development of IWS.

**Findings—**Most papers were prospective observational or interventional studies.

**Conclusions—**Given the state of existing evidence, well-designed prospective studies are required to better characterize IWS in critically ill pediatric patients. This review provides data to

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support the construction of a conceptual model of IWS risk that, if supported, could be useful in guiding future research.

**Keywords**

Sedation; analgesia; dependence; tolerance; iatrogenic withdrawal syndrome; WAT-1; pediatric intensive care unit

## Introduction

Sedation is commonly used in pediatric intensive care to reduce the physiologic and psychological stress associated with critical illness. However, it is known that rapid weaning or abrupt cessation of sedation therapy in drug tolerant children precipitates iatrogenic withdrawal syndrome (IWS)[1] – a cluster of symptoms that can have deleterious effects on patient recovery and hospitalization.[2–4]

The prevailing mechanistic theory of drug tolerance involves receptor desensitization and up-regulation of excitatory intracellular pathways.[5–7] Anand et al. provide a comprehensive review of physiologic mechanisms in pharmacodynamic tolerance.[2] Clinically, tolerance manifests as a need for increased medication to achieve consistent therapeutic effects. Tolerance, escalating doses, and prolonged treatment are coupled with the development of physiologic dependence. Once patients manifest tolerance and dependence, termination of therapy without measured weaning precipitates IWS.[3]

Most studies on opioid and benzodiazepine IWS have focused on characterizing symptoms in the pediatric population, developing screening and assessment tools, or testing treatment regimens. A fundamental question in understanding IWS has been overlooked: what specific factors predispose pediatric intensive care unit (PICU) patients to developing IWS? Knowledge of IWS risk factors and their inter-relationships may help clinicians prevent IWS. We performed a systematic review of the literature to identify all common and salient risk factors associated with IWS, with the intention of building a conceptual model of IWS that will guide future research.

## Methods

PubMed/Medline, EMBASE, CINAHL, and the Cochrane Central Registry of Clinical Trials were searched for original research on opioid- and/or benzodiazepine-related IWS in critically ill children. Given the limited number of studies in this area, time limits were set between January 1, 1980 and August 1, 2014. Corresponding exploded MeSH or EMTREE terms were used when possible (Table 1).

Articles published in English and discussing IWS following either opioid or benzodiazepine therapy in children in intensive care settings were included. Age limits were set from 2 weeks post-gestation to 18 years. Articles were excluded if data about opioid or benzodiazepine treatment were not specified; if primary data were not reported; or if subjects were neonates born to opioid- or benzodiazepine-dependent mothers, children

diagnosed as substance abusers, or subjects with cancer-related pain. Relevant reviews were referenced to capture key studies missed by the search criteria, using ancestry searching.

Study data were extracted into tables of evidence and qualitatively synthesized. Examined data points included study population, location, sample size, sedative medications and mode of administration, IWS assessment method, weaning method, and number and percentage of IWS subjects. For cross-study comparisons, opioid and benzodiazepine doses were converted to morphine and midazolam equivalents. Specifically, morphine equivalent conversion factors to equal 1mg morphine sulfate were as follows: 15μg remifentanil; 15μg fentanyl; 0.15mg hydromorphone; and 0.3mg methadone.[8] Midazolam equivalent conversion factors to equal 1mg midazolam were: 0.2mg clonazepam; 0.3mg lorazepam; and 2mg diazepam. Qualitative analysis of the retrieved articles' results was used to identify both common and novel factors and construct categories of risk. The authors then used an iterative consensus process to develop a conceptual model describing IWS risk that was organized to include patient, process, or system factors contributing to IWS in pediatric patients.

PRISMA guidelines were followed in the conduct and reporting of this study, including consultation with a research librarian in designing the search strategy.[9] Selected studies were evaluated for quality using a criteria-based assessment method for randomized controlled trials (adequacy of randomization and blinding, presence of allocation concealment, and intention-to-treat analysis)[10] and the Newcastle-Ottawa Quality Assessment Scale for observational studies.[11] Randomized controlled trials were rated high, medium and low quality, with a single category deduction for each missing criterion. The Newcastle-Ottawa Quality Assessment Scale assigns star ratings for important elements of observational study design, with a maximum possible score of nine stars. Studies were rated high (7–9 stars), medium (4–6 stars) or low quality (1–3 stars) based on the total number of stars received.

## Results

As outlined in Figure 1, 33 data-based articles met inclusion criteria for this review. Twenty-two studies reported combination opioid and benzodiazepine therapy (Table 2), while 9 reported opioid-only therapy (Table 3), and two reported benzodiazepine-only therapy (Table 4) (Supplemental Digital Content).

The majority of articles (73%) included <50 subjects. The incidence of either opioid- or benzodiazepine-related IWS (Figure 2) was widely variable; for example, frequency of IWS symptoms attributable to cessation of either opioids or benzodiazepines in studies of concurrent therapy ranged from 5%[12] to 87%.[13]

Common themes suggested three categories of risk factors associated with IWS: patient-, process-, and system-level factors, which were synthesized into a conceptual model (Figure 3) that organizes the presentation of evidence in this review. The majority of studies investigated patient-level variables, including age, criticality, duration of therapy and cumulative dose. Process-level factors were directly related to the approach of providing sedation, and included the use of sedation and/or IWS assessment tools and protocols.

System-level factors were infrequently cited, but reflected structural variables that influence clinician practice within the healthcare system, such as interprofessional collaboration and protocol compliance. Each will be presented in the following sections.

## Patient-Level Factors

**Age—**Moderate quality evidence supports a relationship between age and IWS.[14–20] Prospective studies have shown that cumulative opioid dose is related to age,[16] and that younger patients experience higher incidences of IWS.[18] Similarly, among retrospective studies assessing the abrupt cessation of continuous fentanyl[15] or midazolam infusions,[19] younger age was associated with neurologic symptoms of IWS, such as irritability/agitation and seizures.

Older age was also associated with IWS in children.[17] For example, subjects with the highest daily doses (morphine >60 μg/kg/hr or midazolam >250 μg/kg/hr) tended to be older (median 6 years vs. 1.4; $p$=0.0017) even when doses were adjusted for weight.[20] These subjects also had a greater incidence of IWS: 40% of older subjects versus 12% of other subjects ($p \leq 0.001$).

**Criticality—**Limited data from moderate quality studies suggests that severity of illness, particularly involving brain injury or ischemia, contributes to a higher incidence of IWS.[19–24] Low serum albumin concentration in infants receiving midazolam in one retrospective study was associated with IWS-related neurologic disturbances.[19] Several studies noted that children with pre-existing seizure disorders or hypoxemic brain injuries are more likely to experience IWS.[20–23]

**Duration of therapy—**Many studies of varying quality related duration of opioid and/or benzodiazepine therapy to the incidence of IWS.[1,4,8,16,17,25–35] Subjects with longer PICU or hospital lengths of stay,[8,29] more ventilator days,[8,29] and longer ECMO therapy[4,28] were more likely to experience IWS. In one paper, subjects in a randomized trial of methadone-facilitated weaning were more likely to experience treatment failure with longer PICU lengths of stay, particularly after receiving fentanyl for ≥9 days.[29] In two small studies, subjects experiencing IWS received at least 10 days of opioid or benzodiazepine therapy.[34,35]

The majority of studies in this category directly evaluated relationships between length of opioid and/or benzodiazepine therapy and IWS.[1,8,16,17,25–27,30–33,36] Some used statistical methods to establish predictive opioid thresholds, with cut-off lengths of therapy ranging from ≥5[27] to 8 days (OR=18, $p$= 0.02).[25] Exposures longer than 9 days were 100% predictive of IWS.[27] The remaining studies evaluated correlations between length of opioid infusion and IWS outcome or score,[1,16,26,32] which ranged from moderately (r=0.20, $p$=0.02)[1] to strongly positive (r=0.70, $p$<0.05).[26] Among prospective studies investigating the duration of opioid therapy and IWS, all exceeded the 5-day threshold proposed in previous research (Figure 4).[1,8,12,16,17,25–27,30]

No widely accepted threshold duration of therapy for benzodiazepines currently exists, although a recent retrospective study found that a duration of benzodiazepine therapy

exceeding 5 days had 83% sensitivity and 92% specificity for predicting IWS.[36] Positive correlations between duration of benzodiazepine therapy and IWS have been identified in other studies of concurrent opioid and benzodiazepine administration.[1,8,17,30,31] Similar to opioid duration, these correlations are moderate, ranging from r=0.23 ($p<0.01$)[8] to r=0.52 ($p<0.001$).[30] In several prospective studies, subjects with IWS received benzodiazepine therapy in excess of 10 days (Figure 5).[12,21,30,37]

**Dose—**Strong reproducible evidence exists for a relationship between opioid and/or benzodiazepine dose and IWS.[1,4,8,12–14,16,17,20,21,23–30,32,35,36,38–40] Description of dosing varied, with the most common measure being cumulative dose (total amount of drug administered during treatment).

Several studies focused on the association between prescribed opioid dose and IWS risk[4,16,24–28,36,38] Whereas one study found that a cumulative morphine equivalent dose of >106.7mg/kg was associated with 7-fold higher odds of IWS,[28] another identified that a threshold cumulative dose of ≥166.7mg/kg (morphine equivalents) was 100% predictive of IWS.[27] Lower thresholds have also been proposed in unique patient populations, for example, >80mg/kg doses after ECMO support (OR=13.0, $p=0.003$).[4] This threshold had 85% sensitivity and 70% specificity for predicting IWS. A more recent retrospective study found that 32 mg/kg morphine equivalent doses had 83% sensitivity and 85% specificity for predicting IWS in children who received mean cumulative doses of midazolam above published averages.[36]

Only one study of benzodiazepine-associated IWS compared cumulative dose with the incidence of withdrawal,[14] finding that an infusion rate greater than 0.3mg/kg/h (midazolam equivalents) resulted in symptoms consistent with IWS. Cumulative dosages in midazolam equivalents ranged from 0.9mg/kg to 25.3mg/kg,[14] but statistical analyses were not performed. However, in a study of mixed opioid and benzodiazepine administration, a cumulative benzodiazepine dose threshold of >60mg/kg (midazolam equivalents) was significant ($p<0.05$).[23]

Many studies evaluating IWS symptoms attributable to either opioids or benzodiazepines reported dosage associations:[1,8,12,13,17,20,21,23,29–31,34,35,39] one found moderate correlations with opioid dose alone,[31] and four with both opioid and benzodiazepine dose.[1,13,30,36] The remaining studies reported differences between groups with and without IWS in cumulative opioid and/or benzodiazepine doses,[8,12,17,23,29,39] or had too few subjects for statistical analysis.[21,34,35] The prospective studies were graphically compared with the dose thresholds proposed for opioids (Figure 6) and benzodiazepines (Figure 7), respectively. This analysis showed that many studies reported mean or median doses well below the proposed thresholds among subjects with IWS.[1,12–14,17,21,30]

## Process-Level Factors

**Sedation protocol—**Although several authors have noted the importance of standardized sedation protocols in reducing the incidence of IWS,[12,40] little high-quality evidence exists to directly illustrate the proposed relationship. Three studies cited the lack of a sedation management protocol as a risk factor for the development of IWS,[12,31,40] and one moderate-

quality study showed reductions in IWS rates in the intervention groups when sedation protocols were implemented.[12]

**Drug choice:** Some evidence supports an association between drug choice and IWS.[4,13,15,17,20,33,34] Specifically, four studies observed an association between fentanyl and IWS symptoms in children.[4,13,15,41] Rates of IWS are lower in subjects receiving morphine rather than fentanyl infusions (9% v. 57%; $p$=0.01).[4,13] In a retrospective chart review of subjects who developed a "movement disorder" following discontinuation of infusions, fentanyl was the only medication common to all subjects ($p$<0.001).[15]

Methadone has been evaluated in several studies as a potential weaning agent to prevent IWS symptoms in drug-tolerant pediatric patients.[21,22,26,29,33,34,38,41] However, one study[33] determined that the greatest risk factor for IWS among subjects receiving prophylactic methadone was inadequate methadone dosing. Multi-drug sedation therapy has also been proposed as an additional risk factor for IWS.[17,41]

**Mode of administration:** Low to moderate quality articles reported more frequent IWS among subjects receiving continuous infusions of opioids and/or benzodiazepines.[4,15,19,34,35,39,41] Although authors noted that continuous infusions could theoretically contribute to faster development of drug tolerance,[4,19,22] none of the studies in this review specifically compared the effects of intermittent versus continuous administration on the incidence of IWS.

**Weaning:** Fewer than half of the cited studies (37%) utilized a standardized weaning protocol,[4,12,13,22,25,27,29,30,32–34,37] and even with a standard protocol, withdrawal rates ranged from 5%[12,34] to 87%.[13] In the remaining studies, opioids, benzodiazepines, or both were either abruptly discontinued[19,23,24,35] or weaned on a variable basis.[1,8,14–17,20,26,28,31,39–41] Weaning patterns differed substantially: in one prospective study, opioid dose changes in the first 24 hours of weaning ranged from −24mg/kg to +14mg/kg (morphine equivalents).[16] Two studies reported that use of a weaning protocol could reduce the incidence of IWS.[16,38] Some studies abruptly discontinued sedative therapy due to the substitution of other agents, such as clonidine,[16,20,41] dexmedetomidine,[16,39] methadone,[17,21,29,33,34,38,41] or ketamine.[41] Despite prophylactic therapy, IWS still occurred in 5%[34] to 33%[33] of subjects.

**Sedation/withdrawal assessment:** Although many studies of IWS have focused on instrument development,[1,8,13,17,30] few studies have evaluated the influence of routine sedation assessment on the incidence of IWS. Some authors have commented on the issues of over-sedation and development of tolerance,[16,38,40,42] but no studies have specifically evaluated relationships among adequate sedation, standardized assessment, and IWS.

## System-Level Factors

Weaning sedation requires a time-sensitive titration plan that may not be able to be accomplished in the PICU when intensive care beds are limited. In addition, local hospital-based policies may not allow for the use of some sedatives agents outside the PICU. No

paper cited in this review evaluated the impact of PICU census, bed availability, or local policies regarding the use of sedatives in non-ICU areas on the incidence of IWS.

Management of critically ill children also necessitates an interprofessional team approach. Disagreements within the care team regarding optimal sedation can lead to inconsistencies in sedation practices that may predispose children to IWS.[40] Failure of interprofessional collaboration, along with variability in training and experience with sedation management may influence compliance. Poor sedation or weaning protocol compliance has been shown to increase the incidence of IWS.[38]

## Discussion

To date, the strongest risk factors associated with IWS include duration of therapy and cumulative dose. Less evidence exists for relationships with age, criticality, sedation/weaning protocols, and sedation/IWS assessment. This review found few prospective studies offering data specific to opioid- and/or benzodiazepine-related IWS risk factors. It was often necessary to search for any mention of associated risk and extrapolate risk from reported relationships with other variables. The proposed conceptual model (Figure 3) illustrates how the convergence of patient- and process-level factors within a system context may contribute to IWS.

Studies linking the duration of opioid therapy and IWS proposed that a threshold of ≥5 days[25,27] was predictive of IWS (Figure 4). Duration of therapy as a risk factor for benzodiazepine-related IWS has not been demonstrated, although a 5-day[36] to 10-day duration[30] seems contributory (Figure 5). Authors found relationships between cumulative dose of opioid and/or benzodiazepine and duration of infusion,[13,32,34] and cumulative benzodiazepine doses as risk factors,[23] albeit from studies with small sample sizes and inconsistent results. The observed relationship between dose and duration may be too interdependent to determine individual contributions to IWS. For example, a recent study found that the primary outcome of doubling of daily medication dose (tolerance) was more likely to occur with infusions lasting >7 days.[43]

Several studies[4,15,25,26] in this review reported IWS accompanying opioid doses below proposed thresholds, which is potentially attributable to patient-level variability (e.g., pharmacogenetics, body composition, criticality). Similarly, cumulative dose as a risk factor for benzodiazepine-related IWS is not adequately supported in the current literature, as IWS was seen in subjects receiving less than the proposed threshold. Other factors such as criticality may obscure the relationships among dose, duration and IWS. Physiologically, as illustrated in the conceptual model, a patient's therapeutic regimen – medication doses, duration of therapy, and mode of administration – may all act synergistically in contributing to the development of tolerance.

Age, size, and dosing weight are interrelated, so the observation that older children tend to receive higher doses of opioids and benzodiazepines [20] is not surprising. Furthermore, drug metabolism and excretion, and behavioral responses to discomfort, are related to a child's development.[44] Studies in this review included different age ranges, further complicating

this picture. More studies with adequate representation of all age groups are required to demonstrate a more definitive relationship with IWS risk.

Inconsistencies in weaning protocols complicate the analysis of IWS risk, since abrupt cessation or rapid weaning has been shown to precipitate withdrawal symptoms.[2,8,29,42,45] The lower incidence of IWS in studies with specified weaning protocols[12,29,30,37] may be an indication of the importance of a weaning plan on IWS risk. Conversely, the fact that IWS occurred in controlled, prospective studies with standardized weaning protocols[21,33,34] suggests that protocol compliance or failure leading to IWS must be addressed.

Among opioids, fentanyl has a greater potential for inducing tolerance due to its shorter half-life and greater opioid receptor affinity.[2] More articles in this review reported IWS in subjects receiving fentanyl than with any other opioid.[4,13,15,41] In addition, most of the studies that reported IWS in patients receiving continuous infusions also administered fentanyl,[4,15,19,34,39,40] which could be the mechanism driving the proposed relationship between mode of administration and IWS. However, given the prevalence of fentanyl use, higher administered doses of both opioids and benzodiazepines before the start of weaning, and longer durations of therapy,[1,8] other confounding factors may have influenced the outcome of IWS.[13] This review presents evidence indicating that fentanyl is more likely to cause IWS than other opioids, but more research is necessary.

Only half of the studies used validated instruments to assess subjects' IWS.[1,4,8,12,13,16,17,21,22,25–30,38,39] Finnegan's Neonatal Abstinence Score (NAS) tool has not been validated outside of the neonatal population,[46] despite its use in a quarter of the studies in this review. Establishing the validity and generalizability of other IWS assessment instruments is challenging, and studies applying validated IWS assessment tools (e.g. WAT-1,[1,8] SOS[17,47]) are needed. IWS will remain difficult to quantify objectively until biological markers are available.

Analysis of the literature reveals an evolving discussion of IWS risk in terms of tolerance- and non-tolerance-related factors. Drug choice, duration of therapy, mode of administration, and cumulative dose may be substitute measures for tolerance. Age and criticality are patient-level variables that may constitute risks for IWS independent of tolerance. Process-level variables related to clinician decision making, which may be driven by policies of the larger healthcare system, also contribute to IWS risk but not tolerance. However, system-level factors have not been consistently recognized or explored in the existing literature. For example, there is consensus that weaning sedation requires a time-sensitive titration plan that may not be able to be accomplished in the PICU when intensive care beds are limited. Providers may need to move patients out of the PICU as soon as their primary condition has stabilized. In addition, local policies may not allow the use of some sedatives agents in non-ICU areas, further limiting providers' ability to maintain a consistent weaning plan in some children. However, none of these factors were addressed in the articles assembled in this review. Further research is needed to examine the effect of system-level factors on patients' risk for developing IWS.

This study has important limitations. Small sample sizes were problematic for achieving requisite statistical power in several included studies, and the overall quality of the available data was moderate. In addition, due to the authors' limitations, articles published in languages other than English could not be included in this review. This review was performed according to the PRISMA statement, where applicable, although an assessment of the risk of bias for each study was not performed. A registered protocol also was not used in the conduct of this review. A meta-analysis of the selected studies could not be completed, due to low levels of evidence and significant heterogeneity in the populations of the included studies.

## Conclusion

This is the first systematic review of risk factors associated with IWS in the critically ill pediatric population that identifies risk factors at the level of the patient, process, and system, and describes their relationship with the development of tolerance to opioids and benzodiazepines. Of all the factors identified, duration of therapy and cumulative dose are the most predictive of IWS, as has been suggested by other authors. However, this review particularly highlights the need to further explore process and system variables, such as sedation/IWS assessment, and protocol adherence. There are many remaining questions for future studies on risk factors associated with IWS. This model can be used to guide the design and reporting of future studies on IWS in critically ill children.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

Financial support: University of Pennsylvania Hillman Scholar' s Program in Nursing Innovation

We would like to thank the Hillman Foundation for providing support for the doctoral education of K. M. B. as a Hillman Scholar in Nursing Innovation, which included the time spent in developing this manuscript.

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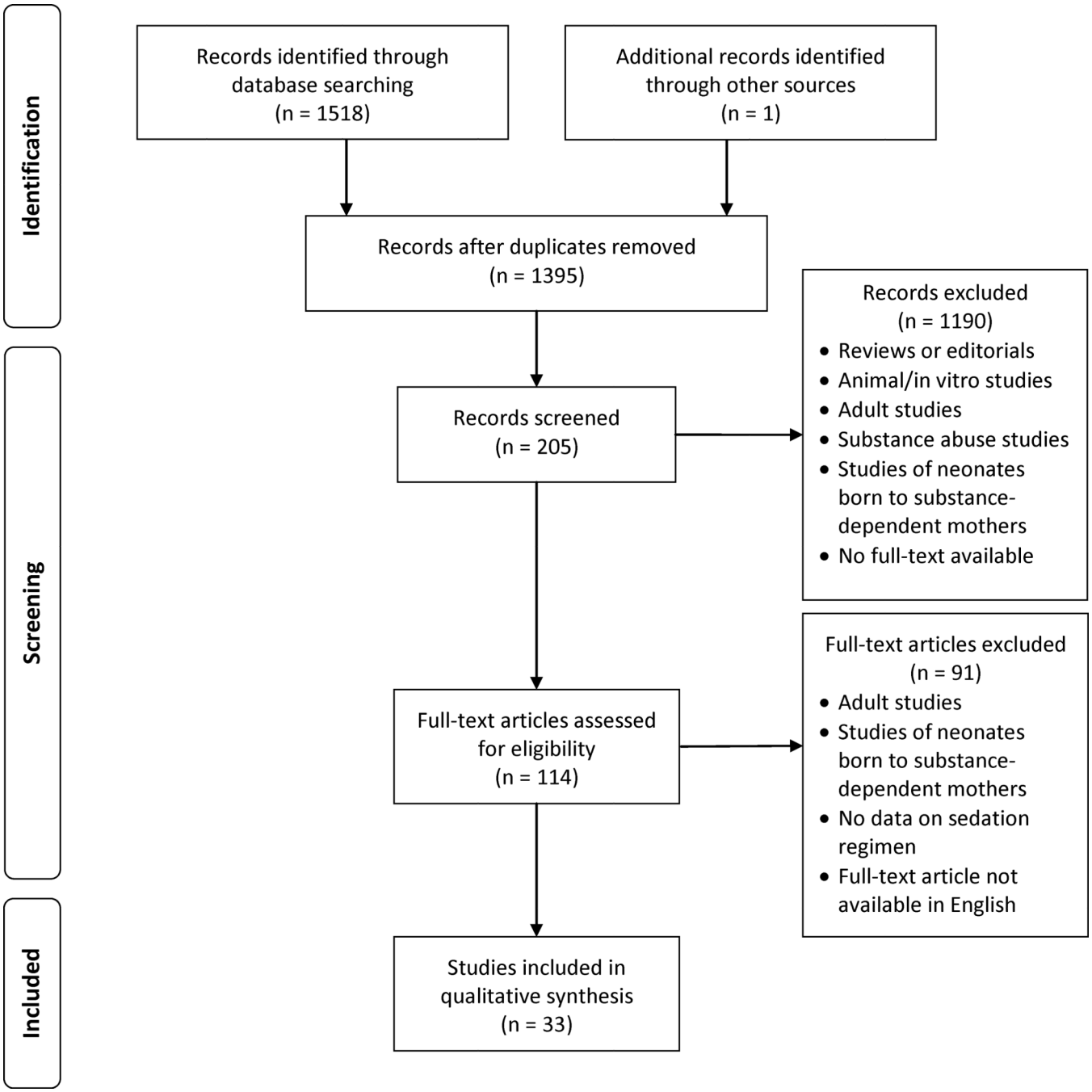


**Figure 1.**
Systematic search and selection process

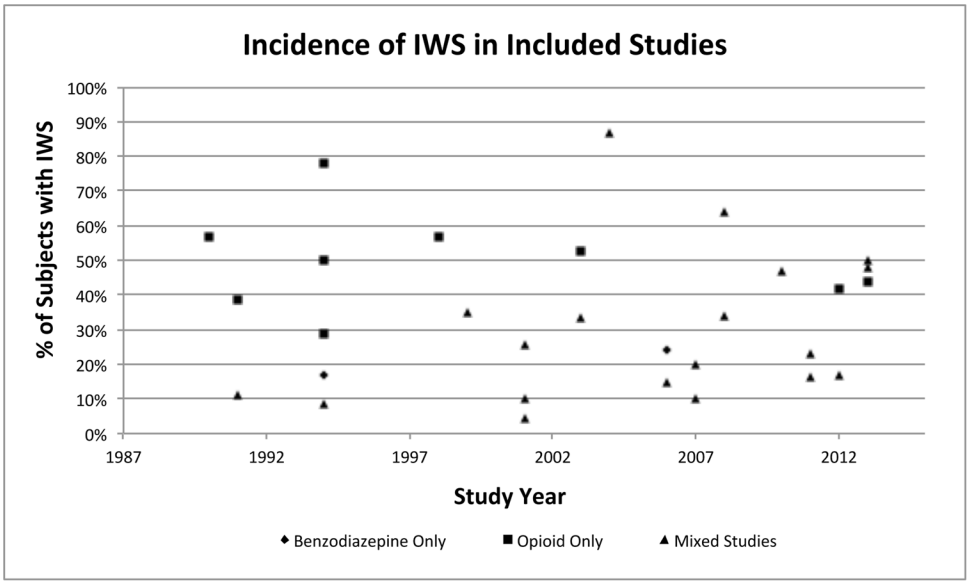


**Figure 2.**

Proportion of subjects with IWS relative to the total number of subjects among included studies (Mixed includes studies where the subjects received both opioids and benzodiazepines.)

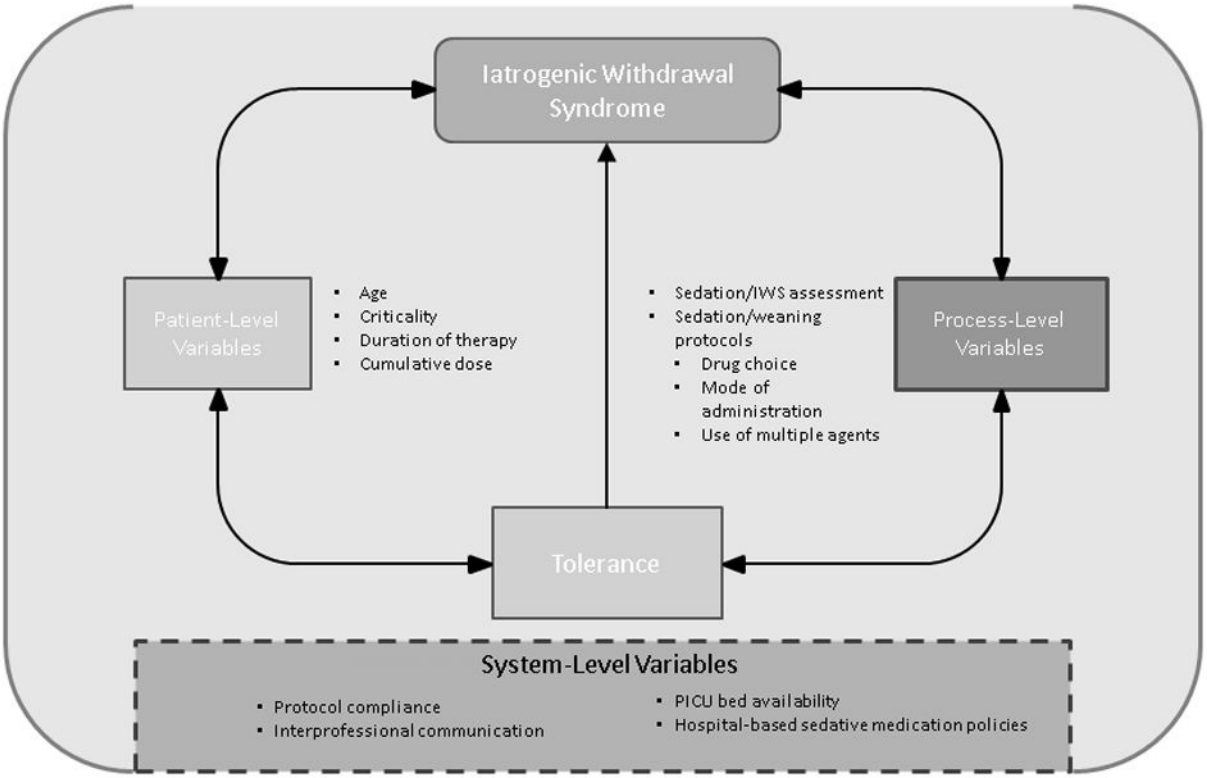


**Figure 3.**

Risk for Iatrogenic Withdrawal Syndrome (IWS). Conceptual model relating three levels of risk factors for IWS in critically ill children

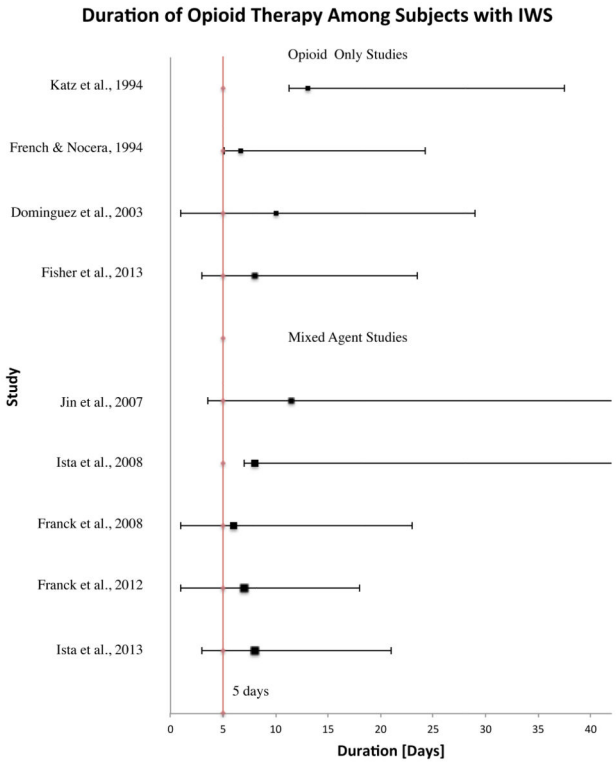


**Figure 4.**

Cross-study comparison of duration of opioid therapy in opioid-only and mixed agent (i.e. opioid and benzodiazepine administration) studies, among subjects with IWS

Reference for 5 day threshold: Katz, Kelly, & Hsi (1994)[27]

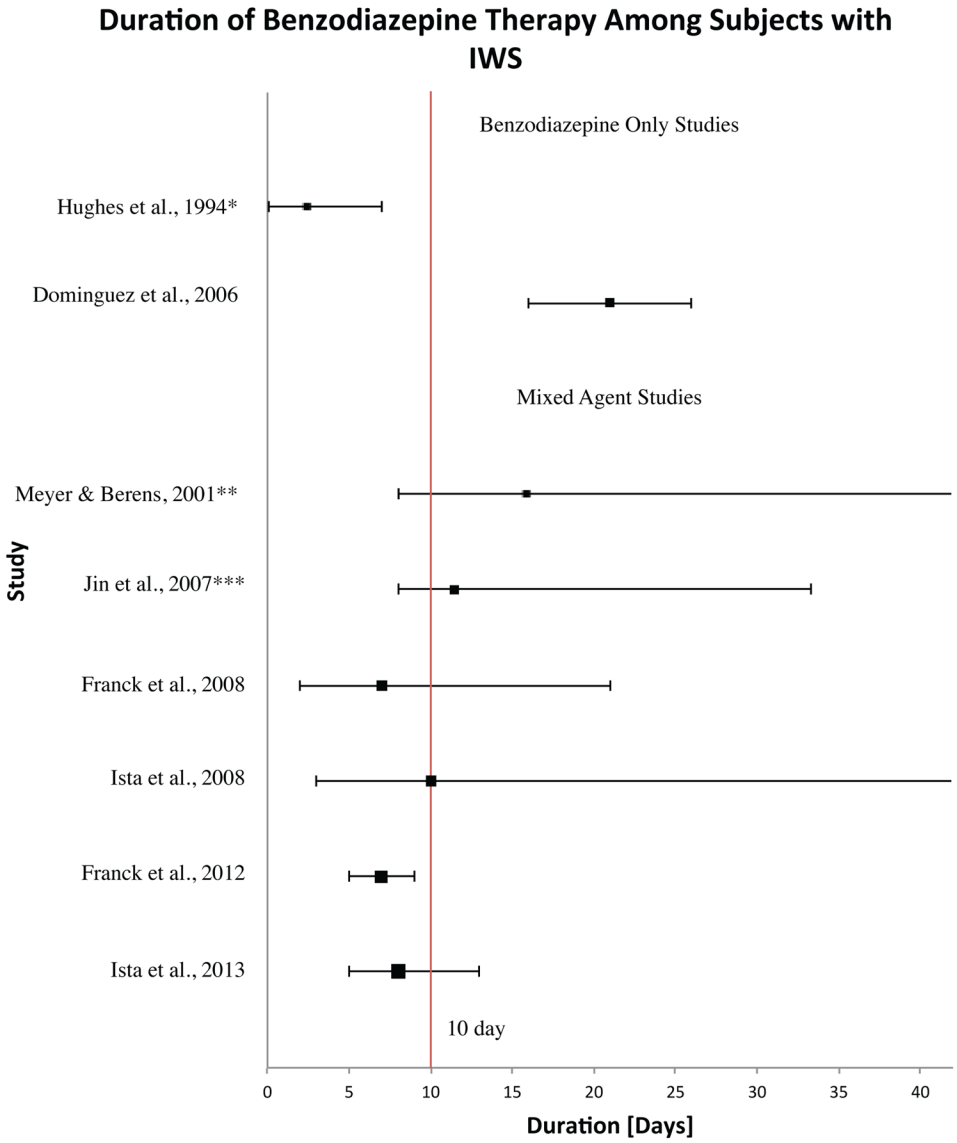


**Figure 5.**

Cross-study comparison of duration of benzodiazepine therapy among subjects with IWS *Duration includes medication taper. **Reported duration only applies to nine patients receiving lorazepam. ***Authors did not specify medication for the listed duration of sedation.

Reference for 10 day threshold: Ista, et al. (2008)[30]

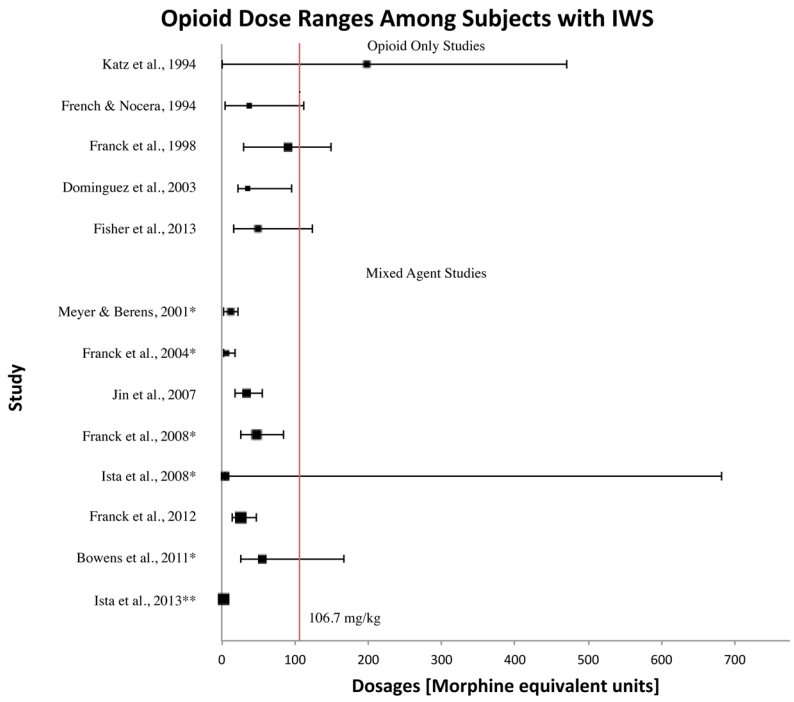


**Figure 6.**

Cross-study comparison of cumulative dose of opioids among subjects with IWS

*Provided dose range for total study group, not IWS subjects specifically. **Values not calculated in original study.

Reference for 106.7 mg/kg (morphine equivalents) threshold: Arnold, Truog, & Orav (1994)[28]

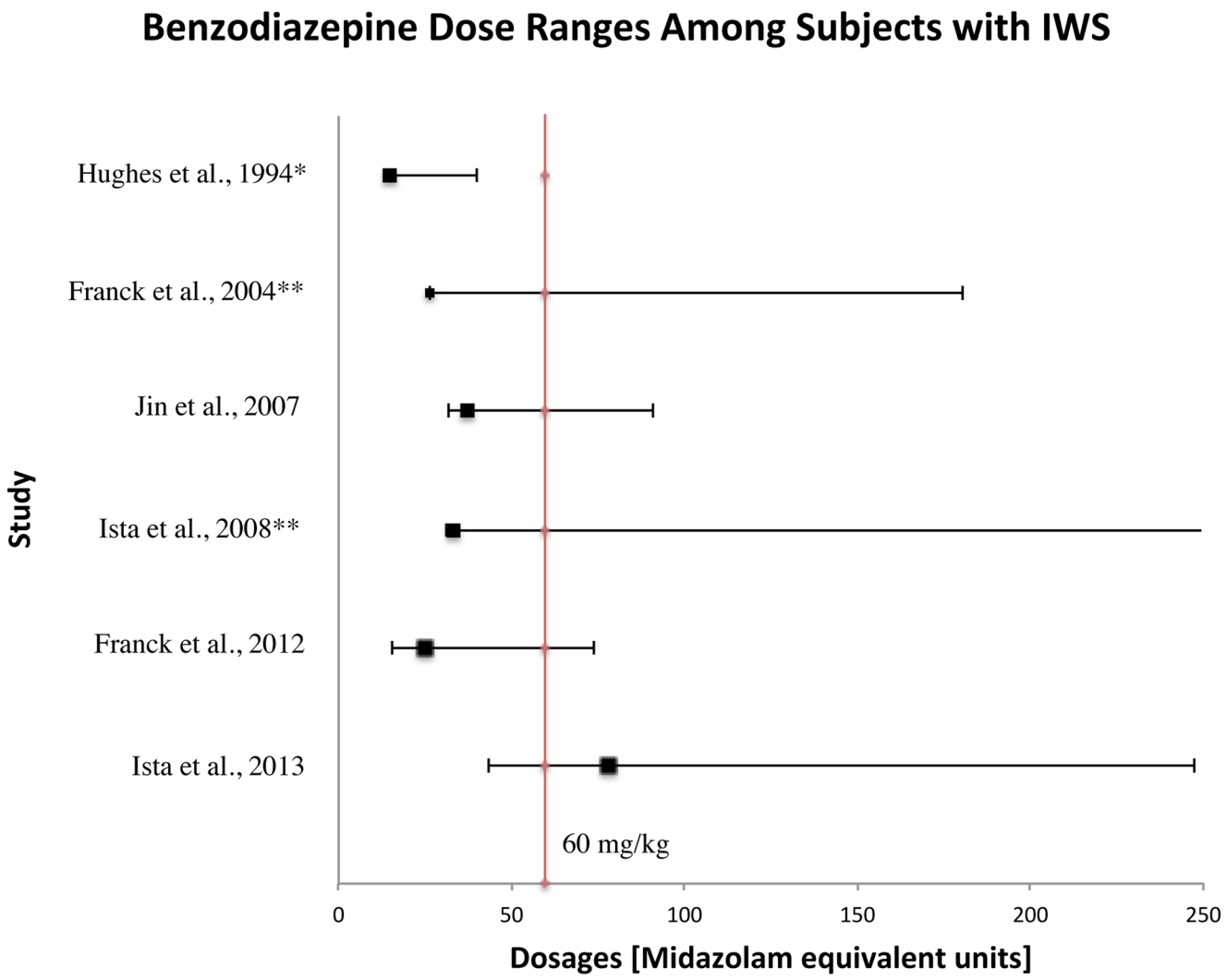


**Figure 7.**

Cross-study comparison of cumulative dose of benzodiazepines among subjects with IWS

*Values not calculated in original study. **Provided dose range for total study group, not IWS subjects specifically.

Reference for 60 mg/kg (midazolam equivalents) threshold: Fonsmark, Rasmussen, & Carl (1999)[23]

## Table 1

Detailed search strategy

| **Medline/PubMed AND CINAHL search strategy for pediatric studies** | |
|---|---|
| **Search** | **Terms** |
| #1 | ventilator* OR ventilation* OR respirator* OR "Respiration, artificial"[Mesh] OR "artificial respiration" |
| #2 | weaning OR weaned OR weans OR wean OR discontinue OR terminat* |
| #3 | hypnotic* OR depressant* OR sedat* OR opioid* OR narcotic* OR benzodiazepine* OR fentanyl OR morphine* OR diazepam OR lorazepam OR midazolam |
| #4 | #1 AND #2 AND #3 |

| **EMBASE search strategy for pediatric studies** | |
|---|---|
| **Search** | **Terms** |
| #1 | “ventilator” OR “ventilation” OR “respirator” OR "artificial respiration" OR artificial ventilation/exp OR assisted ventilation/exp |
| #2 | “weaning” OR “weaned” OR “weans” OR “wean” OR “discontinue” OR “terminate” OR “termination” *[NOTE: No EMTREE term for ventilator weaning]* |
| #3 | “hypnotic” OR “depressant” OR “sedative” OR hypnotic sedative agent/exp OR “opioid” OR “narcotic” OR opiate/exp OR narcotic agent/exp OR “benzodiazepine” OR benzodiazepine/exp OR fentanyl OR morphine OR diazepam OR lorazepam OR midazolam |
| #4 | #1 AND #2 AND #3 |

Filters: English; Child: birth (manual exclusion of < 2 weeks)-18 years

Limits: English; Child: birth (manual exclusion of < 2 weeks)-18 years