Intensive Care Med (2013) 39:16–30
DOI 10.1007/s00134-012-2758-y

REVIEW

**Don-Kelena Awissi**
**Genevieve Lebrun**
**Douglas B. Coursin**
**Richard R. Riker**
**Yoanna Skrobik**

# Alcohol withdrawal and delirium tremens in the critically ill: a systematic review and commentary

Received: 4 June 2012
Accepted: 9 October 2012
Published online: 27 November 2012


**Electronic supplementary material**
The online version of this article (doi:10.1007/s00134-012-2758-y) contains supplementary material, which is available to authorized users.

D.-K. Awissi · G. Lebrun
Pharmacy Department, Hôpital Maisonneuve-Rosemont, 5415 Boulevard de l'Assomption, Montreal, PQ H1T 2M4, Canada

D. B. Coursin
Departments of Anesthesiology and Medicine, University of Wisconsin School of Medicine and Public Health, B6/319 UW CSC, Madison, WI 53792-3272, USA

R. R. Riker
Department of Critical Care Medicine, Maine Medical Center, Tufts University School of Medicine, 22 Bramhall Street, Portland, ME, USA

Y. Skrobik (✉)
Intensive Care Unit, Hôpital Maisonneuve-Rosemont, 5415 Boulevard de l'Assomption, Montreal, PQ H1T 2M4, Canada
e-mail: yoanna.skrobik@umontreal.ca
Tel.: +1-514-8080678
Fax: +1-514-2523806

**Abstract** *Introduction:* Alcohol withdrawal is common among intensive care unit (ICU) patients, but no current practice guidelines exist. We reviewed published manuscripts for prevalence, risk factors, screening tools, prophylactic and treatment strategies, and outcomes for alcohol withdrawal syndrome (AWS) and delirium tremens (DT) in the critically ill. *Methods:* The following databases: PubMed, MEDLINE, Embase, Cochrane Database of Systematic Reviews and Central Register of Controlled Trials, CINAHL, Scopus, Web of Knowledge, pain, anxiety and delirium (PAD) Guidelines REFWORKS, International Pharmaceutical Abstracts and references for published papers were searched. Publications with high or moderate Grading of Recommendations Assessment, Development and Evaluation (GRADE) and Oxford levels of evidence were included. *Results:* Reported AWS rates range from <1 % in 'all ICU comers' to 60 % in highly selected alcohol-dependent ICU patients. Alcohol dependence and a history of withdrawal are significant risk factors for AWS occurrence. No screening tools for withdrawal have been validated in the ICU. The benefit of alcohol withdrawal prophylaxis is unproven, and proposed regimens appear equivalent. Early and aggressive titration of medication guided by symptoms is the only feature associated with improved treatment outcome. *Conclusions:* Treatment of AWS is associated with higher ICU complication rates and resource utilization. The optimal means of identification, prevention and treatment of AWS in order to establish evidence-based guidelines remain to be determined.

**Keywords** Alcohol withdrawal syndrome · Delirium tremens · Alcohol · Critical care · Intensive care · Sedatives · Withdrawal · Delirium

## Introduction

Half of the adult Americans aged 18 years and over are considered to be regular drinkers [1]. Reportedly, 10 % of North Americans are excessive alcohol consumers, while 3 % of Americans self-report experiencing alcohol withdrawal [2]. Excess alcohol use contributes to 20 % of admissions to the intensive care unit (ICU) [3], and

chronic alcoholism may affect as many as 50–60 % of trauma patients [4]. Many of these patients are at risk for developing early alcohol withdrawal syndrome (AWS) [5], particularly those with alcohol dependence (DSM criteria supplement 1). Withdrawal seizures may occur 12–24 h later, while few patients develop delirium tremens (DT), with symptoms including agitation, hallucinations, disorientation, tachycardia, hypertension, fever, agitation, and diaphoresis.

Despite the apparent high frequency among ICU patients, no guidelines for the recognition or management of AWS or DTs in the critically ill have been published. Developing clear evidence-based management directives remains challenging because of inconsistent approaches in individual studies including types of ICU, patient demographics, definitions of AWS risk, prophylaxis and treatment regimens, and outcomes reported.

The objectives of this study were to systematically review the ICU literature to identify AWS risk factors and tools validated for AWS detection, prevention strategies, treatment approaches, and appropriate outcomes among critically ill patients.

## Methods

### Search methodology

The authors developed an initial list of key words related to AWS in the ICU, and a professional librarian (Odette Hinse) expanded this list, developed corresponding medical subject heading terms, and searched relevant clinical databases (search details are in online supplement S2). Given the continuum and overlap between AWS, DTs, and alcohol withdrawal seizures and the limited high-quality data, all forms of alcohol withdrawal were labeled AWS and included in this project. The publications were reviewed focusing on diagnostic criteria (risk factors and screening tools), prevention and treatment protocols and outcomes. Articles could be considered in more than one category. Case reports and series, editorials, narrative reviews, systematic reviews, animal or in vitro studies and letters to the editor were all reviewed. Publications that contained original data were retained; all other publication types were excluded after careful content and reference review.

Quality of evidence was scored using OXFORD criteria (1–5) [6] and Grading of Recommendation Assessment, Development and Evaluation (GRADE) system (high, moderate, or low/very low) [7, 8]. Low and very low GRADE and four and five Oxford level studies were excluded. At least two authors independently performed the quality profile for each study, attaining perfect (100 %) concordance between reviewers for the OXFORD level of evidence. The GRADE criteria were also concordant between reviewers, but not as uniform, likely related to the paucity, inconsistency, and heterogeneity of data. Of 112 eligible articles, 26 were retained for grading based on content. Reviewing the references for all papers identified an additional eight articles. A total of 34 articles met our final search criteria (Fig. 1).

## Results

### Diagnostic criteria

#### *AWS risk factors and incidence*

The identification of explicit risk factors for AWS among ICU patients could not be completed because no study prospectively evaluated all risk factors, and because studies considered different ones. In addition, inclusion criteria were different across studies. Moreover, studies varied by type of hospital and ICU, and prospective prevention or treatment trials did not specify the number of overall ICU admissions to use as a denominator, again making AWS incidence and risk stratification challenging [4, 9–11]. The available incidence data and descriptors of AWS are summarized in Table 1.

Some studies based AWS risk on level of alcohol consumption alone, but with inconsistent thresholds [12–15]. Trauma patients who present with alcohol in their blood are often thought to be at risk for AWS, but when studied, they are not at greater risk for withdrawal; this feature does not correlate with chronic alcohol use [16].

Alcohol consumpion as a predictor for developing AWS is described with varying thresholds and varying classification schemes. A standard alcohol drink is typically defined as 12 grams of alcohol, which is equivalent to 355 ml (12 oz) of beer, 150 ml (5 oz) of wine, or 45 ml (1.5 oz) of 80-proof liquor. Using these definitions, the National Survey on Drug Use and Health 2010 reported that 52 % of Americans older than 12 years of age reported being current drinkers (at least one drink in the past 30 days), 23 % binge drank (five or more drinks on the same occasion, on at least 1 day in the past 30 days) and 6.7 % reported heavy drinking ($\geq$5 drinks on the same occasion on 5 or more days in the past 30 days) [17]. These data contrast with primary care and hospitalized patients, in whom alcohol dependence has been reported to be as high as 20–42 % [18–20]. In an observational study in a group of alcohol-dependent patients (determined with DSM-IV positive and median daily alcohol consumption of >100 grams of alcohol), the incidence of withdrawal seizures and delirium was 17 % before prevention measures could be initiated [21].

Alcohol-dependent patients with a history of prior alcohol withdrawal or those consuming alcohol while being treated for an alcohol related disease constitute the greatest risk for withdrawal symptoms [13].

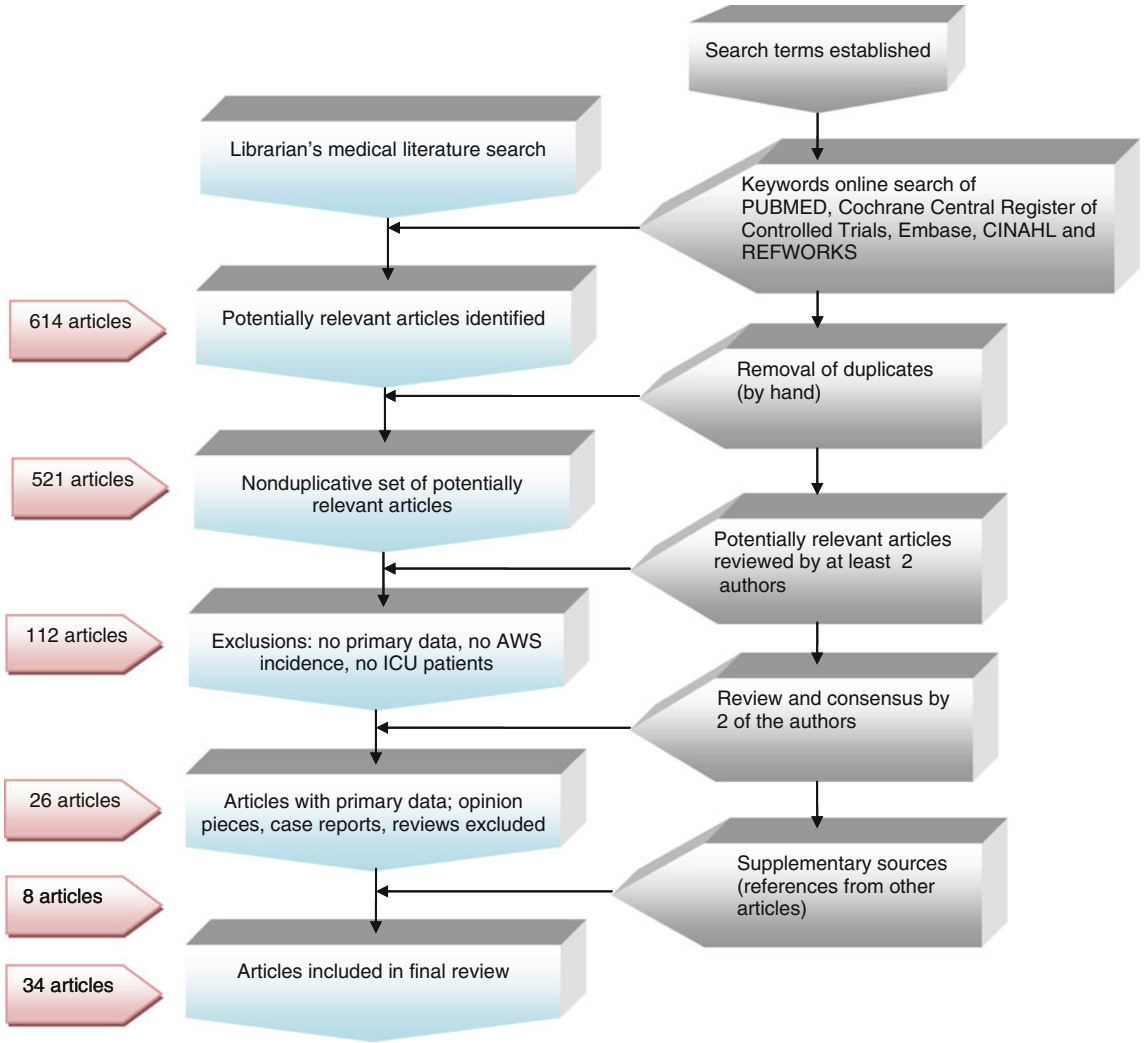


**Fig. 1** Description of search

*Screening tools for AWS*

Several tools have been used to identify patients at risk for AWS including the CAGE questionnaire and the Short Michigan Alcohol Screening test (short-MAST) [22]. The CAGE questionnaire asks patients four questions: Have you ever felt you needed to **C**ut down on your drinking? Have people **A**nnoyed you by criticizing your drinking? Have you ever felt **G**uilty about drinking? Have you ever felt you needed a drink first thing in the morning (**E**ye-opener) to steady your nerves or to get rid of a hangover? Abuse or dependence on alcohol is suggested by $\geq$2 "yes" answers, indicating further investigation is warranted [23, 24]. "Yes" responses to $\geq$3 questions and a daily consumption >60 g define alcohol-dependence or abuse according to DSM-III or IV criteria.

Despite its simplicity, CAGE may be limited in its use in the ICU because of its failure to predict severity of AWS or outcome [25]. Among 652 surgical oncology ICU patients, 24/26 (92 %) with CAGE scores $\geq$1 developed AWS; the two without AWS had CAGE scores of 1 and 3, and drank 4–6 drinks daily. Three patients with CAGE scores of 0 and alcohol intake of 2–8 drinks a day developed AWS [25]. A minority of authors propose considering patients with CAGE scores of 1 or 2 and alcohol consumption of 25–60 g/day social drinkers, combined with a biological marker (carbohydrate-deficient transferrin or CDT) to define alcohol abuse and justify AWS prophylaxis. Unfortunately, little data is available at this time to support the value of biomarkers to define AWS risk [26, 27].

The Short MAST is described in one study that evaluated critically ill patients with acute respiratory distress syndrome and multiple organ dysfunction [28]. Its value in critically ill patients, however, has not been psychometrically validated.

**Table 1** Described incidence of AWS across studies and populations

| Data source | *N* | Alcohol abuse | Alcohol dependence | Alcohol withdrawal |
|---|---|---|---|---|
| USA data bank [57] | 785,602 | 3.4 % | N/A | 0.5 % |
| Data bank review [38] High psychiatric % | 11,651 | | 12 % | 6 % |
| Alcohol detoxification patients [58] | 827 | 100 % | N/A | More if prior seizures (59 vs. 49 %; $p = 0.007$) and structural brain lesions (21 vs. 4 %; $p < 0.001$) |
| Oncology SICU patients with prophylaxis [30] | 32 men | 100 % | 100 % | 41 % |
| Trauma + blood alcohol [59] | 1,751 | N/A | N/A | 5 and 3.9 % |
| Trauma [12] | 431 | 9 % | | 0.5 % |
| Upper GI cancer SICU [9] | 197 men | | | 8 % |
| GI surgery/trauma [10] | 300 | 100 % | 0 | 35 % |
| Elective thoracic and vascular patients [49] | 321 | | 10 % | 12.6 % CAGE ≥2 (1.2 % of total) 1.7 % with CAGE = 0 |
| Inner city ICU patients [40] | 742 | N/A | 12 % | N/A |
| Inner city ICU [41] | 200 | 21 % alcohol related | | 52 % of alcohol related admissions (total 22) |
| Inner city ICU in Ireland [44] | 275 | 12 % alcohol related | | 9 % of alcohol related admissions (total 3 alcohol withdrawal seizures) |

*CAGE* acronym of four questions used for screening of alcoholism, *GI* gastro-intestinal, *SICU* surgical intensive care unit

### *AWS assessment*

Several withdrawal or agitation scales have been used to objectively rate symptom severity in patients experiencing AWS or DT. The revised Clinical Institute Withdrawal Assessment for alcohol scale (CIWA-Ar) and the Sedation Agitation Scale (SAS) are the most frequently described. The CIWA-Ar scale (Table 2) was revised for use in medical ICU patients [29] and used in five studies [4, 9, 10, 29, 30]. A score ≥20 reflects full-blown AWS in most studies [4, 10, 29], while prevention studies targeted varying CIWA scores (10 to <20) and different evaluation intervals (ranging from every 10 min to four times daily) [4, 10, 29, 30]. No study documented a link between frequency of assessments and outcomes, nor addressed the challenges of assessing CIWA-Ar in mechanically ventilated patients. Intubated patients were often excluded [14] or not mentioned at all [4, 11, 31]. Some studies allowed patients intubated after the onset of AWS to remain in the study during withdrawal treatment [10, 16, 32–34], and one study considered mechanical ventilation a complication of AWS treatment [35].

The SAS was used to titrate pharmacologic therapy or as part of an AWS prevention protocol in two publications [14, 33]. A score ≥5 triggered pharmacologic intervention with a therapeutic goal score of 3–4. Titration was required at least every hour if agitation persisted in the treatment trial [33] and adjusted to maintain a score of 4 based on SAS measurements every 4 h in the prevention study [14].

## Prevention

Four single center ICU alcohol withdrawal prevention studies were identified [9, 14, 15, 30]. Criteria for beginning AWS prophylaxis varied from a history of alcohol consumption to alcohol dependence, but used different criteria. Ethanol infusions were monitored in single arm studies [15, 30] or compared to treatment with benzodiazepines, clonidine, or antipsychotic medications [9, 14] applying widely varying administration protocols. Although the rate of ethanol elimination is highly unpredictable in alcohol-dependent patients [15], prophylactic ethanol infusion appeared moderately effective (13/32 patients developed alcohol withdrawal) [30]. An unblinded study compared ethanol to benzodiazepines in chronic alcoholics. The findings suggested similar efficacy since no patient in either arm developed withdrawal [14]. This may have reflected the low-risk of the selected cohort. The effect of four different preventive regimens: flunitrazepam–clonidine, chlomethiazole–haloperidol, flunitrazepam–haloperidol and ethanol, was compared in 197 alcohol dependent patients, with similar rates of withdrawal prevention and ICU length of stay [9]. Appendix 1 provides greater detail on the inclusion criteria and results of the four prevention studies described above.

## Treatment

Ten moderate to high quality treatment studies for alcohol withdrawal in ICU patients were identified, including two prospective, controlled, randomized and blinded studies [4, 10], one prospective but lower quality effort [11], 3 pre-post reports [25, 31, 33], and four single-arm designs [25, 29, 31, 36]. Treatment was primarily benzodiazepine-based [4], [10], [25], [29], [31], [33], [36, 37], including lorazepam [25, 31, 33], flunitrazepam [4, 10, 37], midazolam [31], diazepam [33, 37], and chlordiazepoxide

**Table 2** Revised Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) scale

Patient: _____ Date: _____ Time: _____:_____

Pulse or heart rate, taken for one minute: _____ Blood pressure: ____/____

**Nausea and vomiting.** Ask "Do you feel sick to your stomach? Have you vomited?"
Observation:
0—No nausea and no vomiting
1—Mild nausea with no vomiting
2—
3—
4—Intermittent nausea with dry heaves
5—
6—
7—Constant nausea, frequent dry heaves, and vomiting

**Tremor.** Ask patient to extend arms and spread fingers apart.
Observation:
0—No tremor
1—Tremor not visible but can be felt, fingertip to fingertip
2—
3—
4—Moderate tremor with arms extended
5—
6—
7—Severe tremor, even with arms not extended

**Paroxysmal sweats**
Observation:
0—No sweat visible
1—Barely perceptible sweating; palms moist
2—
3—
4—Beads of sweat obvious on forehead
5—
6—
7—Drenching sweats

**Anxiety.** Ask "Do you feel nervous?"
Observation:
0—No anxiety (at ease)
1—Mildly anxious
2—
3—
4—Moderately anxious or guarded, so anxiety is inferred
5—
6—
7—Equivalent to acute panic states as occur in severe delirium or acute schizophrenic reactions

**Agitation**
Observation:
0—Normal activity
1—Somewhat more than normal activity
2—
3—
4—Moderately fidgety and restless
5—
6—
7—Paces back and forth during most of the interview or constantly thrashes about

**Tactile disturbances.** Ask "Do you have you any itching, pins-and-needles sensations, burning, or numbness, or do you feel like bugs are crawling on or under your skin?"
Observation:
0—None
1—Very mild itching, pins-and-needles sensation, burning, or numbness
2—Mild itching, pins-and-needles sensation, burning, or numbness
3—Moderate itching, pins-and-needles sensation, burning, or numbness
4—Moderately severe hallucinations
5—Severe hallucinations
6—Extremely severe hallucinations
7—Continuous hallucinations

**Auditory disturbances.** Ask "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?"
Observation:
0—Not present
1—Very mild harshness or ability to frighten
2—Mild harshness or ability to frighten
3—Moderate harshness or ability to frighten
4—Moderately severe hallucinations
5—Severe hallucinations
6—Extremely severe hallucinations
7—Continuous hallucinations

**Visual disturbances.** Ask "Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?"
Observation:
0—Not present
1—Very mild sensitivity
2—Mild sensitivity
3—Moderate sensitivity
4—Moderately severe hallucinations
5—Severe hallucinations
6—Extremely severe hallucinations
7—Continuous hallucinations

**Headache, fullness in head.** Ask "Does your head feel different? Does it feel like there is a band around your head?"
Do not rate for dizziness or lightheadness; otherwise, rate severity.
0—Not present
1—Very mild
2—Mild
3—Moderate
4—Moderately severe
5—Severe
6—Very severe
7—Extremely severe

**Orientation and clouding of sensorium.** Ask "What day is this? Where are you? Who am I?"
Observation:
0—Orientated and can do serial additions
1—Cannot do serial additions or is uncertain about date
2—Date disorientation by no more than two calendar days
3—Date disorientation by more than two calendar days
4—Disorientated for place and/or person

Total score: _____ (maximum = 67) Rater's initials _____

Adapted from Sullivan et al. [60]

[33, 37]. Drug combinations in these studies included benzodiazepines, antipsychotics (haloperidol), chlomethiazole, phenobarbital, clonidine, propofol, carbamazepine, and valproate [4, 10, 25, 33, 35].

*Protocol and symptoms driven treatment*

Three groups evaluated the impact of using standardized protocols for AWS treatment [25, 31, 33]. Protocol-driven

management was associated with less benzodiazepine use ($p = 0.014$), and lower complication rates (intubation, excessive sedation) but similar hospital and ICU length of stay in a study of 36 medical ICU patients [31]. Symptom-triggered therapy for resistant alcohol withdrawal in 96 ICU patients was associated with higher benzodiazepine doses but a significant reduction in mechanical ventilation ($p = 0.008$) [33] and transfers to the ICU for AWS-related causes were significantly decreased in patients with head and neck cancer treated with a protocol ($p = 0.03$) [25].

Several treatment studies linked specific clinical withdrawal symptoms with triggered medication administration [11, 25, 36]. Lansford grouped them into three distinct clusters that prompted different drug classes to treat AWS: central nervous system excitation (anxiety, restlessness, being bothered by bright lights or sounds) was treated with benzodiazepines; adrenergic hyperactivity (nausea or vomiting, tremor, sweating, hypertension, tachycardia, premature beats) was treated with clonidine; and delirium was treated with haloperidol [25]. A drug and symptom class-based protocol in surgical ICU patients treated with symptom-driven boluses of clonidine, haloperidol, and flunitrazepam suggested this protocolization decreased severity and duration of alcohol withdrawal symptoms ($p \leq 0.01$), and led to shorter ICU and ventilation duration ($p \leq 0.01$) [10].

A study of 159 trauma ICU patients compared the combinations of flunitrazepam-clonidine, chlomethiazole-haloperidol, or flunitrazepam–haloperidol [4]. The chlomethiazole–haloperidol group had significantly more pneumonia ($p = 0.04$) and longer mechanical ventilation duration ($p = 0.03$), while the flunitrazepam–clonidine group experienced significantly more cardiac complications ($p = 0.005$) [4, 10].

The rapidity of withdrawal symptom manifestation and the speed of progression to full-blown withdrawal syndrome, if left untreated, were emphasized in several studies [31, 33, 36]. Aggressive treatment within the first 8–24 h appears crucial to ensure rapid symptom control, with no trial addressing optimal timing and frequency of assessments.

Appendix 2 summarizes patient characteristics and AWS treatments considered in the treatment portion of this review.

### Outcomes

Studies describing alcohol withdrawal and delirium tremens necessarily include alcohol dependent patients. No study, however, compared alcohol consumers to alcohol dependent patients, or contrasted these two groups with occasional drinkers or abstainers, in order to stratify complication risk categories. Alcohol dependent patients are reported to have higher infection, sepsis and septic shock rates [38], are more likely to get admitted to the ICU and die in the hospital [39], and cost more in hospital resource dollars than patients not admitted to ICU for alcohol-related problems [32]. The few studies that addressed co-variates emphasized a high rate of ICU admission attributable to alcohol-related diagnoses, but once admitted, their length of stay and costs were no different from non-alcoholic medical [3] or trauma [40] patients.

Financial estimates varied greatly in methods, but an episode of alcohol withdrawal cost $7,462 per patient for benzodiazepines and ICU monitoring in one study [36], while among patients admitted for alcohol-related problems, the cost of an ICU stay was significantly higher in the alcoholic group ($52,527) compared to non-alcoholics ($43,136) [41]. Implementing AWS management guidelines is associated with a reduction in benzodiazepine acquisition costs and ICU length of stay [37].

Discrepancies in reported outcomes for various drinking intensity categories may relate to different definitions of risk, with some studies finding no differences between at risk and non-at-risk drinkers in ICU morbidity or mortality [39, 42], while patients with acute respiratory distress syndrome had worse outcomes if they regularly consumed alcohol [28]. Patients admitted to ICU with alcohol related complications (cirrhosis, GI bleed, intoxication, withdrawal) had a longer length of stay and higher mortality if more than one alcohol-related clinical feature contributed to their ICU admission [43, 44] or if chronic illness or delirium were present or mechanical ventilation required [43, 45].

Not surprisingly, critically ill trauma patients developing AWS have a longer duration of mechanical ventilation and ICU stay, more frequent pneumonia, urinary tract infections, sepsis, and septic shock, and higher mortality [46]. These adverse events may be associated with alcohol use, but immune down-regulation has also been associated with the pharmacological effects of morphine, propofol and benzodiazepines [47]. Patients experiencing AWS require more frequent tracheostomy and PEG feeding tubes, and require higher doses of sedation [48, 49], which has been associated with prolonged mechanical ventilation and length of stay [50–52].

Long term outcome data are sparse, but patients admitted to the ICU for DT are often seen again in the emergency room within two years related to AWS or alcohol related complications [53]. Appendix 3 presents the outcomes extracted from included studies.

## Discussion

Despite an estimated prevalence of chronic alcoholism affecting up to 20–40 % of hospitalized patients and 50–60 % of trauma patients, little high-quality data for how best to prevent, diagnose, and treat AWS in the ICU is available and ICU-specific guidelines have not been published.

Methods to identify ICU patients at risk for AWS include alcohol related questionnaires (CAGE), alcohol consumption documentation, the Short MAST, and a history of prior AWS or seizures, while the reliability of biochemical markers such

as CDT has yet to be determined. The relative validity of these variables has not been compared. A prior history of alcohol withdrawal and seizures should be considered a significant risk for AWS, though this information may not be obtainable in all patients. Asking patients or next of kin about alcohol consumption and withdrawal may stratify patients at risk for AWS or DT, and facilitate recognition of the need for prompt titrated pharmacological management.

Risk thresholds in prevention studies vary widely, and best prevention pharmacotherapy has not been defined. The threshold between prevention studies for patients at risk or with minor symptoms and treatment studies with more significant AWS components is often been blurred, and clearer definitions are needed.

Once withdrawal occurs, early and frequent assessment of withdrawal symptoms is essential, particularly in the first 24–48 h. The CIWA-Ar relies on patient communication for information regarding nausea/vomiting, anxiety, tactile and auditory disturbances, and headache. This tool may not be applicable or reliable in critically ill patients, particularly in mechanically ventilated patients. Titrating treatment or prophylaxis to agitation symptoms such identified with the SAS in general ICU patients, and with CIWA-Ar whenever feasible, appears the best approach to match drug dosing and symptom severity and improve outcomes.

Benzodiazepines are a mainstay of AWS treatment, despite uncertainty about their effectiveness and safety. Barbiturates and propofol appear safe and effective GABA alternatives for AWS. Clonidine as a combination regimen is efficacious in reducing the adrenergic symptoms of AWS, and combination therapy with benzodiazepines, alpha-2 agonists and antipsychotics was associated with good outcomes in multiple studies [10, 25]. Dexmedetomidine is structurally similar to clonidine; however, AWS management with this drug is limited to case reports [54]. Its usefulness as adjunctive therapy to benzodiazepines has been reported [55]. Although best practices in prevention and treatment strategy cannot be established given the limited evidence and inconsistent designs, combination pharmacotherapy, titrated to symptom severity and linked to symptom clusters appears promising.

Published ICU studies of patients with AWS have reported inconsistent outcomes since they have applied highly variable definitions. The standardization of definitions for AWS will facilitate future comparisons and systematic reviews. In addition to standard patient demographics and history of alcohol ingestion, additional beneficial data should include whether an ICU admission was for AWS or other critical illness, whether the study was intended for prevention or treatment, what monitoring tools were applied, and what the thresholds were for each pharmacologic intervention and what triggered their administration. The ICU-related complications such as sepsis, pneumonia, mechanical ventilation, ARDS, duration of ICU and ventilator therapy, and discharge location should also be sought.

Several limitations of our manuscript deserve comment. Because of limited high quality data, we combined research addressing various forms of AWS from different types of ICUs using different study populations, designs, thresholds for treatment, AWS prevention or treatment protocols, and patient outcomes. This variability highlights the need for more uniform research approaches to this complex area before treatment guidelines based on evidence can be proposed. Delirium, a common and morbid complication of critical care admission, is both a risk factor and a potential confounder for alcohol withdrawal symptoms which we were not able to address [45]. In addition, our filtering process was qualitative by necessity, but our consensus between authors is likely to have reduced potential bias.

Significant gaps remain in the current literature, and these should stimulate future studies. The detection of withdrawal or risk for AWS in mechanically ventilated patients, particularly when no history is available from the patient, has not been studied. Patients presenting with psychomotor slowing rather than agitation have largely been ignored in the critical care setting [56]. Additional gaps in knowledge that require study include identification of the optimal methods to stratify risk for alcohol withdrawal and delirium tremens in various populations, establishing whether prophylaxis in high-risk patients is beneficial and safe, determining whether prophylactic ethanol administration best serves this purpose, comparative trials of alcohol withdrawal treatment, and outcome studies that consider the many confounders (alcohol consumption among them) likely to blur the link between alcohol withdrawal and outcomes. Finally, whether adverse events are related to alcohol consumption, dependence, withdrawal, patient co-morbidities, or the treatment for AWS remains unclear.

## Conclusion

Early detection of alcoholic patients at risk for AWS should be routine for ICU patients, and is likely best performed based on identifying a history of heavy alcohol consumption and prior withdrawal events. Early and aggressive treatment with combination therapy regardless of pharmacologic agents such as benzodiazepines, alpha-2 agonists, and anti-psychotics should be titrated to specific withdrawal symptoms. Outcomes should be stratified by alcohol use, alcohol withdrawal, and concomitant co-morbidities, and should provide extended follow-up and ongoing efforts towards alcohol detoxification and abstinence. Large prospective trials in critically ill patients, particularly those who are intubated and mechanically ventilated, are needed to evaluate the best tools to assess the presence and the severity of acute withdrawal syndrome and the optimal pharmacologic approaches for prevention and treatment.

**Acknowledgments** The authors wish to thank Odette Hinse, Hôpital Maisonneuve Rosemont, Dr Lavinius Alexander Ungur, Klinik für Anästhesiologie mit Schwerpunkt operative Intensivmedizin, Charite Berlin, Germany, for initial discussions in Oxford rating methodology, and Dr Claudia Spies for her support.

**Conflicts of interest** No conflicts of interest to declare.

## Appendix 1

See Table 3.

**Table 3** Description of prevention studies

| References | Design | Population, *N* | Inclusion criteria | Aim of study | Medication | Outcomes |
|---|---|---|---|---|---|---|
| Eggers et al. [30] | Prospective observational; post hoc analysis | 32 T & GI SICU | Alcohol dependence (DSM-IV), daily ethanol consumption ≥60 g and diagnostic indicators of alcoholism: CAGE questionnaire, MCV, GGT, CDT | Does BEC predict AWS prophylaxis effectiveness | Ethanol infusion | 41 % (13) pt developed AWS. Total ethanol dose and ethanol levels measured did not differ between the success and failure groups |
| Spies et al. [9] | Prospective randomized blinded | 197 HNT and GI cancer SICU | Alcohol-dependent (DSM-IIIR) pt, ethanol consumption ≥60 g/day + indicators of alcoholism: CAGE questionnaire, MCV, GGT, CDT, ASAT, ALAT | Comparison of four pharmacologic prophylactic regimens | Bolus and IV infusion of: FZP/CLO or CMZ/HAL or FZP/HAL or IV ethanol | ICU LOS, AWS prevention and complications = same except more tracheo-bronchitis in CMZ/HAL group ($p = 0.0023$) |
| Weinberg et al. [14] | Prospective randomized | 50 T ICU | History of chronic daily alcohol consumption ≥5 beverage/day for at least 6 months up to the day of admission | IV ethanol vs. BZD prevention efficacy | IV ethanol vs. DZP to SAS; Failure → DZP (if ethanol group) and neu-roleptics (if DZP/ethanol) | Ethanol = more agitation (87.9 % deviation from calm and cooperative; 81.4 % in BZD). 1 failure in ethanol group |
| Wilkens et al. [15] | Retrospective | 11 SICU | Alcoholic pt who had admitted alcohol dependence | Are forensic data ethanol pharmacodynamics transferrable to therapeutic ethanol substitution | IV ethanol; Bolus based on weight + estimated Vd. Target BEC: 0.6 g/L; infusion titrated to BEC of 0.5–0.7 g/L | No AWS in 10/11 pt; 95 % CI for EER: 20.6–34,4 mg/dl per h; different from forensic EER of 15 mg/dl per h ($p = 0.0014$) |

*ALAT* alanine aminotransferase Test, *ASAT* aspartate aminotransferase Test, *AWS* alcohol withdrawal syndrome, *BEC* blood ethanol concentration, *BZD* benzodiazepine, *CAGE* acronym of four questions used for screening of alcoholism, *CDT* carbohydrate-Deficient Transferrin, *CLO* clonidine, *CMZ* clomethiazole, *DSM* diagnostic and statistical manual of mental disorders, *DZP* diazepam, *EER* ethanol elimination rate, *FZP* flunitrazepam, *GGT* gamma-glutamyl transpeptidase, *GI* gastro-intestinal, *HAL* haloperidol, *HNT* head and neck tumor, *ICU* intensive care unit, *LOS* length of stay, *MCV* mean corpuscular volume, *pt* patients, *SAS* riker scale, *SICU* surgical intensive care unit, *T* trauma, *Vd* volume of distribution

## Appendix 2

See Table 4.

**Table 4** Description of treatment studies

| Reference | Study design | Population, *N* | Inclusion criteria | Aim of study | Medication | Outcomes |
|---|---|---|---|---|---|---|
| DeCarolis et al. [31] | Retrospective observational | 36 MICU veterans | Diagnosis of AWS | AWS outcomes with sx driven BZD protocol vs. standard BZD infusion | Pre: historical control; post LZP IV according to pt response | MINDS ≤20 (pre vs. post): 19.4 vs. 7.7 h ($p = 0.002$); mean dose: 1,677 vs. 1,044 mg ($p = 0.014$); infusion time: 122 vs. 52 h ($p = 0.001$); complications:44 vs. 25 % |
| Elsing et al. [11] | Prospective randomized controlled | 26 MICU | Alcoholic pt with clinical AWS. No inclusion/ exclusion criteria specified | CMZ vs. GHB for AWS | CMZ vs. GHB IV Only CLO permitted in the first 7 h.; then others prn (CMZ, BDZ, HAL) | AWS score modified at 3 h GHB vs. CMZ ($p = 0.021$); ICU LOS similar (4.1 vs. 5 days) No serious side effects |
| Eyer et al. [35] | Retrospective cohort study | 847 pt for alcohol detoxification | Pt admitted for alcohol detoxification with a discharge diagnosis code for alcohol intoxication, withdrawal syndrome or alcohol delirium tremens and moderate to severe AWS. All pt included fulfilled the ICD-10 criteria of alcohol dependence | CBZ or VPA in addition to standardized symptom-triggered therapy | CBZ OR VPA with CMZ for all. CLO and HAL prn plus thiamine | Severity of AWS not different CBZ: longer LOT and LOS, higher single and cumulative doses of CMZ, higher needs for CLO, required ICU more often, more withdrawal seizure and adverse reactions. Withdrawal seizure as the cause of admission predictor of withdrawal seizure (OR 2.61; 95 % CI 1.43–4.78; $p = 0.002$) |
| Gold et al. [33] | Retrospective cohort study | 96 MICU | Pt admitted to the ICU solely for the treatment of severe AWS (DSM criteria) | Standard vs. symptom-triggered AWS | Pre: Sx-triggered per doctor Post: protocol; DZP then phenobarbital then propofol prn | Reduced MV ($p = 0.008$); 2 fold increase in DZP dose in the first 24 h; three fold increase in DZP max. doses; more phenobarbital (58 vs.17 %; $p < 0.001$) |
| Hoey et al. [36] | Retrospective observational study | 57 MICU | Hospital admission for AWS, documentation of one or more signs of the disorder, and treatment with BZD | BZD patterns for AWS; drug selection and costs based on drug acquisition and LOS in ICU | – | 90 % in ICU within 24 h; BZD LOT: 6.2 ± 5.5 days; ICU LOS: 3.9 ± 2.7 days; LZP (80 % inappropriately treated with LZD could have been treated with another BZD); maximum LZP on day 3, at 81.9 ± 107.7 mg/pt; BZD $1008.72 ± $ 54.45/pt. ICU $6453.40 ± 2586.38/pt |
| Hoey et al. [37] | Prospective observation study with pre-post data | 50 MICU | Hospital admission for AWS, documentation of one or more signs of the disorder, and treatment with BZD | BZD prescribing habits, BZD dosage and costs, cost of ICU LOS and assess compliance to guidelines | CDP, DZP or LZP or combination of CDP, MDZ and/or LZP | 76 % (38) appropriate use of CDP. Use of CDP increased after guideline ($p < 0.0002$). CDP $ per pt: $61.74 ($0.03–585.98). For pt on CDP, ICU and hospital LOS: 1.1 day (0–9 days) and 5.6 days (1–17 days). Pre-post data: BZD dosages similar. BZD $ per pt ≈ 20 fold ($1008.72 vs. $59.79). Hospital LOS similar, ICU LOS reduced (4.1 vs. 1.1 days; $p < 0.0001$) |

**Table 4** continued

| Reference | Study design | Population, *N* | Inclusion criteria | Aim of study | Medication | Outcomes |
|---|---|---|---|---|---|---|
| Lansford et al. [25] | Prospective cohort study retrospective cohort control | 26 HNT SICU | HNT pt with AWS (AWS Type Indicator), and reported alcohol intake of at least 1 to 2 drinks daily or CAGE questionnaire score >0 | Benefit of standardized protocol for identification, characterization and treatment of AWS | Pre-protocol: n/a Post: Type A sx (score ≥1), LZP q1 h; Type B sx (score ≥1) CLO q3 h prn x2; Type C sx (score ≥1), HAL q2 h prn X2 | Preop. identification of pt at risk for postop. AWS in 92 % of subjects ($n = 24$) (92 % sensitivity, 99 % specificity); Unexpected AWS 11 % ($n = 3$); All AWS 2.45 %; cost: $2,306 pre-protocol vs. $3,393 post); Transfers (ward to ICU): pre vs. post. 29 % ($n = 4$) vs. 4 % ($n = 1$) ($p = 0.03$) |
| Spies et al. [9] | Prospective randomized double-blinded controlled | 44 (T and GI) SICU | Pt who developed AWS (CIWA-Ar >20), possible alcohol abuse (DSM-IV), alcohol consumption >60 g/day and diagnostic indicators of alcoholism: CAGE questionnaire, MCV, CDT, liver function tests and complete cell count | Bolus (BTG) vs. continuous infusion titrated therapy group (ITG) on severity and duration of AWS | Open: CIWA-Ar driven bolus CLO, H, FZP; FZP in all. BLINDED: CIWA-Ar/ RASS driven ITG:HAL and CLO + placebo boluses of FZP,CLO, HAL BTG: Placebo HAL and CLO + boluses of FZP, CLO, HAL NOT BLINDED: (ITG and BTG) propofol prn | Decreased AWS severity and duration with BTG ($p \leq 0.01$) Higher FZP, CLO and HAL in ITG ($p \leq 0.01$) Propofol use same (ITG vs. BTG). In pt who required propofol, # boluses ($p = 0.01$) and dose ($p = 0.03$) higher in ITG ICU LOS shorter in BTG ($p \leq 0.01$) MV duration halved and pneumonia lower in BTG vs. ITG ($p \leq 0.01$) |
| Spies et al. [4] | Prospective randomized controlled partly blinded | 159 T ICU | Alcohol-dependent (DSM-IIIR) who developed AWS (CIWA-Ar >20 + diagnosis confirmed by neurology consultant + diagnostic indicators of alcoholism: CAGE questionnaire, sMAST, blood alcohol concentration, CDT, MCV, GGT, AST, ALT hemoglobin, hematocrit) | 3 AWS regimens on ICU outcomes | Bolus of FZP or CMZ and CLO and HAL (goal = CIWA-Ar <20); then Rx adjusted to CIWA-Ar <10 with infusion of FZP/CLO or CMZ/HAL or FZP/HAL | ICU LOS no different CMZ/ HAL = more pneumonia ($p = 0.0414$) and prolonged MV ($p = 0.0315$) More cardiac complications in FZP/CLO group ($p = 0.0047$) |
| Watling et al. [29] | Descriptive protocol development and implementation | MICU | Pt admitted to a medical ICU for sx management and monitoring of AWS (definition of AWS: based on a modified version of the CIWA-Ar scale developed) | Coordinate AWS care, objectively measure AWS signs, BZD based on AWS sx | Modified CIWA-Ar developed and implemented. BZD scale for required LZP doses | Perceptions of protocols by staff. No outcomes. No validation of the modified withdrawal scale |

*ALAT* alanine aminotransferase Test, ASAT aspartate aminotransferase test, *WS* alcohol withdrawal syndrome, *BZD* benzodiazepine, *CAGE* acronym of four questions used for screening of alcoholism, *CBZ* carbamazepine, *CDP* chlordiazepoxide, *CDT* carbohydrate-deficient transferrin, *CIWA-Ar* revised clinical institute withdrawal assessment for alcohol scale, *CLO* clonidine, *CMZ* clomethiazole, *DSM* diagnostic and statistical manual of mental disorders, *DZP* diazepam, *FZP* flunitrazepam, *GGT* gamma-glutamyl transpeptidase, *GHB* gamma-hydroxy-butytic acid, *GI* gastro-intestinal, *HAL* haloperidol, *HNT* head and neck tumor, *LOS* length of stay, *LOT* length of treatment, *LZP* lorazepam, *MCV* mean corpuscular volume, *MICU* medical intensive care unit, *MINDS* Minnesota detoxification scale, *MDZ* midazolam, *MV* mechanical ventilation, *pt* patients, *SICU* surgical intensive care unit, *sx* symptoms, *T* trauma, *VPA* valproate, *WD* withdrawal

## Appendix 3

See Table 5.

**Table 5** Outcomes

| References | Population, *N* | Aim of study | Results |
|---|---|---|---|
| Baldwin et al. [32] | All medical and surgical admissions; $N = 435$ | Frequency and costs of adult ICU admissions related to substance abuse | 9 % (41) alcohol related-13 % ICU costs Male and uninsured status = higher rates of substance abuse-related admission |
| Bard et al. [12] | Level 1 trauma pt ≥ 15 years old with ISS (injury severity scores) < 16 (minor and moderate trauma; $N = 6431$ | Effect of AWS on LOS, morbidity, mortality and cost | AWS incidence 0.9 % AWS a/w: more ICU days (7.58 vs. 3.30; $p < 0.0001$), ventilator days (6.79 vs. 3.47; $p = 0.008$), LOS (15.8 days vs. 4.85; $p < 0.0001$), respiratory failure (23.6 vs. 1.4 %; $p < 0.0001$), pneumonia (18.2 vs. 1.1 %; $p < 0.0001$), UTI (9.1 vs. 1.8 %; $p = 0.0005$), sepsis (7.3 vs. 0.3 %; $p < 0.0001$), higher cost with AWS $p < 0.000$ |
| De Wit et al. [57] | Records: Nationwide Inpatient Sample (NIS) 2002-2003. $N = 785{,}602$ > 18 years old with pneumonia, sepsis, GI bleeding, asthma, COPD or respiratory failure. AUD and MV based on the NIS | Is a co-diagnosis of AUD a/w risk of MV as well as MV duration? | Pneumonia and COPD 38.2 and 20.3 % of pt -AUD were mostly young, male, African American or native American and very ill<br>3.4 % (26,577 pt) AUD and 0.5 % (3,967 pt) AWS<br>8.3 MV. 53 % for <96 h and 47 % ≥96 h<br>AUD associated with MV (OR 1.49) when adjusted for co-variates, but not with duration of MV. AWS increased duration of MV (OR 1.48) |
| Gacouin et al. [39] | Adult ICU pt with stay ≥3 days with assessable alcohol consumption and active treatment; Mixed ICU (MICU and liver tx); $N = 358$ evaluable pt | To determine if excessive alcohol consumption (EAC) increases ICU-acquired bacterial infection risk. EAC: >14 drinks/week or >4 drinks per occasion in men ≤65 years old and 7 drinks/week or >3 drinks per occasion for women >65 years old | 31 % at-risk drinkers; 55 % intake of >5 drinks/day<br>SMAST scores >3 = 34 % in pt <5 drinks/day; 92 % in pt >5 drinks/day<br>ICU mortality higher in at-risk drinkers (23 vs. 13 %; $p = 0.011$)<br>36 % at-risk with bacterial infections vs. 19 % ($p < 0.001$); highest >5 drinks/day ($p = 0.048$). After covariate adjustment, at-risk drinking a/w bacterial infection at any site (HR 1.92; 95 % CI 1.17–3.14; $p = 0.009$) and VAP (hazard ratio 1.76; 95 % CI 1.05–3.06; $p = 0.04$) |
| Jurkovich et al. [42] (only data relevant to AWS was presented in this table) | Level 1 regional trauma center.Blunt or penetrating T pt ≥18 years old | Chronic alcohol abuse and complications | $N = 285$ with positive SMAST (≥3) and abnormal GGT.<br>Chronic alcohol abuse on both biochemical and behavioral measures = two fold complication risk for pneumonia (OR 1.70; 95 % CI 0, 98–2.97), any infection (OR 2.11; 95 % CI 1.39–3.21) and ICU admission (OR 0.89; 95 % CI 0.62–1.30) |
| McKenny et al. [44] | Mixed ICU inner city in Ireland. 33 pt admitted as a result of alcohol misuse (cirrhosis, coma, intoxication, trauma, pancreatitis, seizures, medical conditions related to alcohol) | To quantify the workload which was the direct result of alcohol misuse | Out of 275 admissions over a 6 months period, 12 % (33) met the inclusion criteria. ICU LOS doubled in the alcohol misuse group (12.3 days). Study group occupied 16.7 % of the total available bed-days during the study period. 30 day mortality was 24.4 % compared to 19 % in the non-study group |

**Table 5** continued

| References | Population, *N* | Aim of study | Results |
|---|---|---|---|
| Maxson et al. [49] | Pt who had planned elective vascular or thoracic procedures and who had planned ICU recovery were screened for alcohol abuse or dependence (CAGE ≥2)<br>31 pt on 321 with positive CAGE | To determine whether alcohol abuse or dependence is a risk factor for peri-operative complications, increased duration of hospital stay, and increased, utilization of nursing | Pt with a CAGE score ≥2 had a significantly increased rate of alcohol withdrawal (12.9 vs. 1.7 %; $p = 0.006$), were readmitted more frequently to an ICU (19.4 vs. 7.9 %; $p = 0.047$), and required sedation more often (32.3 vs. 13.5 %; $p = 0.014$) than those in the non alcoholic group.<br>No significant differences in the LOS or in utilization of nursing resources |
| Monte et al. [43] | AWS admitted to medicine/surgical wards (11 year study); 539 AWS in 436 pt | Clinical variables associated with the risk of dying and the causes of death during the course of AWS in a general hospital | AWS led to admission in 62.3; 37.6 % admitted<br>AWS:41 % with seizures; 48.5 % progressed from AWS to DT<br>ICU transfer rate 37.8 % (49 % in DT pt) for uncontrollable agitation 78.5; 7.8 % for iatrogenic respiratory depression<br>69.9 % of ICU pt intubated for 9.6 days<br>Mortality (6.6 % overall) a/w (1) underlying liver disease (all liver function evaluations)(OR steatosis = 2.3; OR cirrhosis = 4.8); (2) delirium at diagnosis (OR = 2.5); (3) underlying chronic pathology (OR = 3.5); (4) intubation, especially with ICU acquired pneumonia (OR = 8.0) |
| Moss et al. [28] | Part 1 (retrospective): 351 consecutive pt over 8 years with 1 of 7 diagnoses a/w ARDS (sepsis, pancreatitis, transfusion, aspiration, abdominal and chest trauma and multiple fractures)<br>Part 2 (prospective): 220 septic shock pt from 4 university medical centers | Link between chronic alcohol abuse and the development of ARDS | 351 pt with one of 7 diagnoses; 34 % with chronic alcohol abuse. 43 % of the alcohol abusers pt developed ARDS vs. 22 % w/o; s.s. after logistic regression adjustment for at-risk diagnoses, gender and APACHE-II<br>In-hospital mortality higher in chronic alcohol abuser ARDS patients (65 %) compared to non-abusers (36 %) (s.s). Of 220 sepsis pt, 30 % with chronic alcohol abuse (SMAST score ≥3). ARDS 70 % in a pt with chronic alcohol abuse vs.31 % ($p < 0.001$). Abusers had more severe aggregate non-pulmonary organ dysfunction. More abusers had SOFA scores ≥9 (59 vs. 40 %; $p = 0.3$)<br>All ARDS pt survived; hospital LOS longer for ARDS survivors with chronic alcohol than for those with a SMAST score <3 (35 vs. 24 days; $p < 0.05$) |
| O'Brien et al. [38] | Adult ICU admitted ≥1 ICU day<br>*N* = 11, 651 | Association between alcohol dependence (alcoholism not in remission and/or AWS) and sepsis, septic shock and hospital mortality among ICU pt | Alcohol dependence associated with sepsis (multivariate): adjusted OR 1.54 (95 % CI 1.25–1.91; $p < 0.01$); with septic shock: unadjusted OR 1.75 (95 % CI 1.25–2.45; $p = 0.01$) (significant after risk adjustment); with higher odds of hospital mortality (unadjusted analyses): OR 1.28 (95 % CI 1.04–1.57; $p = 0.022$) (significant after risk adjustment); with significantly increased hospital mortality among septic pt: OR 1.46 (95 % CI 1.01–2.11). Pt with alcohol dependence, sepsis and liver disease had 6x higher adjusted odds for hospital mortality<br>LOS and discharge location not described |
| Spies et al. [5] | Male pt with carcinomas of the upper GI tract admitted to the ICU following tumor resection<br>*N* = 213 | Is ICU stay prolonged in chronic alcoholics following tumor resection of the upper GI tract, and are pneumonia, sepsis and death increased in ICU | 121 chronic alcoholics; 39 social drinkers; 61 non-alcoholics; APACHE-III or MOF similar. ICU LOS prolonged by 8 days in chronic alcoholics; MV prolonged |

| | Pneumonia | Sepsis | Death | Surgery | Complications |
|---|---|---|---|---|---|
| Operations | | | | | |
| Chronic alcoholics | 38 % | 13 % | 7 % | 8 % | 23 % |
| Social drinkers | 10 % | 0 % | 0 % | 0 % | 8 % |
| Non-alcoholics | 7 % | 0 % | 0 % | 0 % | 7 % |

**Table 5** continued

| References | Population, *N* | Aim of study | Results |
|---|---|---|---|
| | | | All results s.s.<br>Alcohol-dependent pt (Prophylaxis (P) vs. Treatment (T) of AWS) ($n = 70$) compared to chronic abuse pt (CA) ($n = 51$):<br>CAGE score: 3.4 P vs. 2.6 T vs. 2.4 CA<br>ICU stay: 5 P vs. 19 days T vs. 6 days CA<br>Pneumonia: 15 % P vs. 82 %T vs. 41 % CA<br>Sepsis: 6 % P vs. 32 % T vs. 42 % CA<br>Death: 4 % P vs. 18 % T vs. 6 % CA |
| Spies et al. [46] | 102 male T pt in ER and then ICU over 2.5 years.<br>2 groups: pt with daily alcohol intake ≤25 g and a CAGE = 0 vs. chronic alcoholic pt (DSM-III-R and ICD-10 criteria for alcohol abuse/dependence)<br>Alcohol-dependent pt were either treated with pharmaco-prophylaxis to<br>counteract AWS or if AWS developed were managed accordingly | Whether ICU stay is prolonged in chronic alcoholics with T and whether the complication rate in ICU is increased | Chronic alcoholic (C-A) ($N = 69$)<br>Non-alcoholics (N-A) ($N = 33$)<br>Blood alcohol concentration upon admission, GGT and CDT: all higher in C-A<br>Sensitivity and specificity of CDT and GGT 55 % and 31 %. TRISS, APACHE-II or MOF scores similar on admission. ICU longer in the C-A group with a median difference of 9 days ($p = 0.0003$)<br>Complications: 196 vs. 70 % C-A vs. N-A ($p = 0.000$)<br>Death: 23 vs. 12 % C-A vs. N-A<br>Tracheobronchitis: 75 C-A vs. 45 % N-A; $p = 0.0031$<br>OR for pneumonia: 2.5 (95 % CI 1.7–3.9); sepsis 2.6 (95 % CI 1.3–5.2); bleeding disorders 3.0 (95 % CI 1.4–6.4); cardiac disorders 1.3 (95 % CI 0.6–2.8); mortality 2.2 (95 % CI 0.7–7.1)<br>AWS: 15 pt in the C-A group received pharmacoprophylaxis and did not develop AWS; 42 did. AWS pt had delirium or hallucination/5 pt had vegetative withdrawal syndrome |
| Suchyta et al. [40] | All ICU medical and surgical pt between 1 of July 2003 and 30 of June 2004 $N = 742$ | Comparison of mortality and discharge disposition in ICU pt with and without substance dependence or psychiatric disorders | 742 critically pt included (mean age 49.6, 54 % male, 5.5 % developed ARDS, hospital mortality 21 %, APACHE II 16.5, MV 5.0 days, ICU LOS 7.3 days and hospital LOS 12.3 days)<br>19 % (137) pt substance dependent; younger (45 vs. 51), male (67 vs. 51 %), lower prevalence of ARDS (2 vs. 6 %) and shorter hospital LOS (10 vs. 13 days)<br>Lower rate of sepsis, stroke, cancer and higher rate of drug overdose and GI disease<br>No mortality or discharge disposition difference; substance dependence predicted hospital LOS after controlling for covariates (psychiatric disorders predicted hospital mortality). Trauma a/w alcohol but not drug dependence |

*APACHE* Acute Physiology and Chronic Health Evaluation, *ARDS* acute respiratory distress syndrome, *AUD* alcohol use disorder, *AWS* alcohol withdrawal syndrome, *a/w* associated with, *CAGE* acronym of four questions used for screening of alcoholism, *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *ER* emergency room, *HR* hazard ratio, *ICU* Intensive Care Unit, *LOS* length of stay, *MOF* multiple organ failure score, *MV* mechanical ventilation, *OR* odds ratio, *pt* patients, *SMAST* short Michigan alcohol screening test, *SOFA* sequential organ failure assessment score, *s.s.* statistically significant, *sens.* sensitivity, *spec* .specificity, *TRISS* trauma score - injury severity score, *tx* transplant, *UTI* urinary tract infection, *VAP* ventilated acquired pneumonia, *w/o* without

## References


1. Summary Health Statistics for US Adults: National Health Interview Survey, 2010 Schiller JS, Lucas JW, Ward BW, Peregoy JA (2012) Summary health statistics for US adults: National Health Interview Survey, 2010. National Center for Health Statistics. Vital Health Stat 10(252):91–91, 185
2. Caetano R, Clark CL, Greenfield TK (1998) Prevalence, trends, and incidence of alcohol withdrawal symptoms: analysis of general population and clinical samples. Alcohol Health Res World 22:73–79
3. Uusaro A, Parviainen I, Tenhunen JJ, Ruokonen E (2005) The proportion of intensive care unit admissions related to alcohol use: a prospective cohort study. Acta Anaesthesiol Scand 49:1236–1240
4. Spies CD, Dubisz N, Neumann T, Blum S, Muller C, Rommelspacher H, Brummer G, Specht M, Sanft C, Hannemann L, Striebel HW, Schaffartzik W (1996) Therapy of alcohol withdrawal syndrome in intensive care unit patients following trauma: results of a prospective, randomized trial. Crit Care Med 24:414–422
5. Spies CD, Nordmann A, Brummer G, Marks C, Conrad C, Berger G, Runkel N, Neumann T, Muller C, Rommelspacher H, Specht M, Hannemann L, Striebel HW, Schaffartzik W (1996) Intensive care unit stay is prolonged in chronic alcoholic men following tumor resection of the upper digestive tract. Acta Anaesthesiol Scand 40:649–656
6. Oxford center for evidence based medicine. http://www.cebm.net
7. Atkins D, Eccles M, Flottorp S, Guyatt GH, Henry D, Hill S, Liberati A, O'Connell D, Oxman AD, Phillips B, Schunemann H, Edejer TT, Vist GE, Williams JW Jr (2004) Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches The GRADE Working Group. BMC Health Serv Res 4:38
8. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schunemann HJ (2008) GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 336:924–926
9. Spies CD, Dubisz N, Funk W, Blum S, Muller C, Rommelspacher H, Brummer G, Specht M, Hannemann L, Striebel HW et al (1995) Prophylaxis of alcohol withdrawal syndrome in alcohol-dependent patients admitted to the intensive care unit after tumour resection. Br J Anaesth 75:734–739
10. Spies CD, Otter HE, Huske B, Sinha P, Neumann T, Rettig J, Lenzenhuber E, Kox WJ, Sellers EM (2003) Alcohol withdrawal severity is decreased by symptom-orientated adjusted bolus therapy in the ICU. Intensive Care Med 29:2230–2238
11. Elsing C, Stremmel W, Grenda U, Herrmann T (2009) Gamma-hydroxybutyric acid versus clomethiazole for the treatment of alcohol withdrawal syndrome in a medical intensive care unit: an open, single-center randomized study. Am J Drug Alcohol Abuse 35:189–192
12. Bard MR, Goettler CE, Toschlog EA, Sagraves SG, Schenarts PJ, Newell MA, Fugate M, Rotondo MF (2006) Alcohol withdrawal syndrome: turning minor injuries into a major problem. J Trauma 61:1441–1445 (discussion 1445–1446)
13. Dissanaike S, Halldorsson A, Frezza EE, Griswold J (2006) An ethanol protocol to prevent alcohol withdrawal syndrome. J Am Coll Surg 203:186–191
14. Weinberg JA, Magnotti LJ, Fischer PE, Edwards NM, Schroeppel T, Fabian TC, Croce MA (2008) Comparison of intravenous ethanol versus diazepam for alcohol withdrawal prophylaxis in the trauma ICU: results of a randomized trial. J Trauma 64:99–104
15. Wilkens L, Ruschulte H, Ruckoldt H, Hecker H, Schroder D, Piepenbrock S, Leuwer M (1998) Standard calculation of ethanol elimination rate is not sufficient to provide ethanol substitution therapy in the postoperative course of alcohol-dependent patients. Intensive Care Med 24:459–463
16. Craft PP, Foil MB, Cunningham PR, Patselas PC, Long-Snyder BM, Collier MS (1994) Intravenous ethanol for alcohol detoxification in trauma patients. South Med J 87:47–54
17. https://nsduhweb.rti.org. Accessed 17 January 2012
18. Mayo-Smith MF (1997) Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline. American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. JAMA 278:144–151
19. Gerke P, Hapke U, Rumpf HJ, John U (1997) Alcohol-related diseases in general hospital patients. Alcohol Alcohol 32:179–184
20. Smothers BA, Yahr HT, Ruhl CE (2004) Detection of alcohol use disorders in general hospital admissions in the United States. Arch Intern Med 164:749–756
21. Foy A, Kay J, Taylor A (1997) The course of alcohol withdrawal in a general hospital. QJM 90:253–261
22. Selzer ML, Vinokur A, van Rooijen L (1975) A self-administered Short Michigan Alcoholism Screening Test (SMAST). J Stud Alcohol 36:117–126
23. Ewing JA (1984) Detecting alcoholism. The CAGE questionnaire. JAMA 252:1905–1907
24. Dhalla S, Kopec JA (2007) The CAGE questionnaire for alcohol misuse: a review of reliability and validity studies. Clin Invest Med 30:33–41
25. Lansford CD, Guerriero CH, Kocan MJ, Turley R, Groves MW, Bahl V, Abrahamse P, Bradford CR, Chepeha DB, Moyer J, Prince ME, Wolf GT, Aebersold ML, Teknos TN (2008) Improved outcomes in patients with head and neck cancer using a standardized care protocol for postoperative alcohol withdrawal. Arch Otolaryngol Head Neck Surg 134:865–872
26. Spies CD, Emadi A, Neumann T, Hannemann L, Rieger A, Schaffartzik W, Rahmanzadeh R, Berger G, Funk T, Blum S et al (1995) Relevance of carbohydrate-deficient transferrin as a predictor of alcoholism in intensive care patients following trauma. J Trauma 39:742–748
27. McKinzie BP, Worrall CL, Simpson KN, Couillard DJ, Leon SM (2010) Impact of elevated per cent carbohydrate-deficient transferrin at hospital admission on outcomes in trauma patients. Am Surg 76:492–496
28. Moss M, Burnham EL (2003) Chronic alcohol abuse, acute respiratory distress syndrome, and multiple organ dysfunction. Crit Care Med 31:S207–S212
29. Watling SM, Fleming C, Casey P, Yanos J (1995) Nursing-based protocol for treatment of alcohol withdrawal in the intensive care unit. Am J Crit Care 4:66–70
30. Eggers V, Tio J, Neumann T, Pragst F, Muller C, Schmidt LG, Kox WJ, Spies CD (2002) Blood alcohol concentration for monitoring ethanol treatment to prevent alcohol withdrawal in the intensive care unit. Intensive Care Med 28:1475–1482

31. DeCarolis DD, Rice KL, Ho L, Willenbring ML, Cassaro S (2007) Symptom-driven lorazepam protocol for treatment of severe alcohol withdrawal delirium in the intensive care unit. Pharmacotherapy 27:510–518
32. Baldwin WA, Rosenfeld BA, Breslow MJ, Buchman TG, Deutschman CS, Moore RD (1993) Substance abuse-related admissions to adult intensive care. Chest 103:21–25
33. Gold JA, Rimal B, Nolan A, Nelson LS (2007) A strategy of escalating doses of benzodiazepines and phenobarbital administration reduces the need for mechanical ventilation in delirium tremens. Crit Care Med 35:724–730
34. Lee JH, Jang MK, Lee JY, Kim SM, Kim KH, Park JY, Kim HY, Yoo JY (2005) Clinical predictors for delirium tremens in alcohol dependence. J Gastroenterol Hepatol 20:1833–1837
35. Eyer F, Schreckenberg M, Hecht D, Adorjan K, Schuster T, Felgenhauer N, Pfab R, Strubel T, Zilker T (2011) Carbamazepine and valproate as adjuncts in the treatment of alcohol withdrawal syndrome: a retrospective cohort study. Alcohol Alcohol 46:177–184
36. Hoey LL, Nahum A, Vance-Bryan K (1994) A retrospective review and assessment of benzodiazepines in the treatment of alcohol withdrawal in hospitalized patients. Pharmacotherapy 14:572–578
37. Hoey LL, Nahum A, Vance-Bryan K (1994) A prospective evaluation of benzodiazepine guidelines in the management of patients hospitalized for alcohol withdrawal. Pharmacotherapy 14:579–585
38. O'Brien JM Jr, Lu B, Ali NA, Martin GS, Aberegg SK, Marsh CB, Lemeshow S, Douglas IS (2007) Alcohol dependence is independently associated with sepsis, septic shock, and hospital mortality among adult intensive care unit patients. Crit Care Med 35:345–350
39. Gacouin A, Legay F, Camus C, Volatron AC, Barbarot N, Donnio PY, Thomas R, Le Tulzo Y (2008) At-risk drinkers are at higher risk to acquire a bacterial infection during an intensive care unit stay than abstinent or moderate drinkers. Crit Care Med 36:1735–1741
40. Suchyta MR, Beck CJ, Key CW, Jephson A, Hopkins RO (2008) Substance dependence and psychiatric disorders are related to outcomes in a mixed ICU population. Intensive Care Med 34:2264–2267
41. Marik P, Mohedin B (1996) Alcohol-related admissions to an inner city hospital intensive care unit. Alcohol Alcohol 31:393–396
42. Jurkovich GJ, Rivara FP, Gurney JG, Fligner C, Ries R, Mueller BA, Copass M (1993) The effect of acute alcohol intoxication and chronic alcohol abuse on outcome from trauma. JAMA 270:51–56
43. Monte R, Rabunal R, Casariego E, Lopez-Agreda H, Mateos A, Pertega S (2010) Analysis of the factors determining survival of alcoholic withdrawal syndrome patients in a general hospital. Alcohol Alcohol 45:151–158
44. McKenny M, O'Beirne S, Fagan C, O'Connell M (2010) Alcohol-related admissions to an intensive care unit in Dublin. Ir J Med Sci 179:405–408
45. Ouimet S, Kavanagh BP, Gottfried SB, Skrobik Y (2007) Incidence, risk factors and consequences of ICU delirium. Intensive Care Med 33:66–73
46. Spies CD, Neuner B, Neumann T, Blum S, Muller C, Rommelspacher H, Rieger A, Sanft C, Specht M, Hannemann L, Striebel HW, Schaffartzik W (1996) Intercurrent complications in chronic alcoholic men admitted to the intensive care unit following trauma. Intensive Care Med 22:286–293
47. Sanders RD, Hussell T, Maze M (2009) Sedation and immunomodulation. Crit Care Clin 25:551–570, ix
48. de Wit M, Wan SY, Gill S, Jenvey WI, Best AM, Tomlinson J, Weaver MF (2007) Prevalence and impact of alcohol and other drug use disorders on sedation and mechanical ventilation: a retrospective study. BMC Anesthesiol 7:3
49. Maxson PM, Schultz KL, Berge KH, Lange CM, Schroeder DR, Rummans TA (1999) Probable alcohol abuse or dependence: a risk factor for intensive-care readmission in patients undergoing elective vascular and thoracic surgical procedures. Mayo Perioperative Outcomes Group. Mayo Clin Proc 74:448–453
50. Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, Taichman DB, Dunn JG, Pohlman AS, Kinniry PA, Jackson JC, Canonico AE, Light RW, Shintani AK, Thompson JL, Gordon SM, Hall JB, Dittus RS, Bernard GR, Ely EW (2008) Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet 371:126–134
51. Kress JP, Pohlman AS, O'Connor MF, Hall JB (2000) Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 342:1471–1477
52. Carson SS, Kress JP, Rodgers JE, Vinayak A, Campbell-Bright S, Levitt J, Bourdet S, Ivanova A, Henderson AG, Pohlman A, Chang L, Rich PB, Hall J (2006) A randomized trial of intermittent lorazepam versus propofol with daily interruption in mechanically ventilated patients. Crit Care Med 34:1326–1332
53. Camacho Oviedo JA, Soriano Cuesta C, Manzanares Gomez J, Cachafeiro Fucios L, Oliveros Fonseca M, Garcia Hernandez R, Jimenez Lendinez M (2010) Manifestations and clinical course of delirium tremens in the ICU. Crit Care 14:S166
54. Hoy SM, Keating GM (2011) Dexmedetomidine: a review of its use for sedation in mechanically ventilated patients in an intensive care setting and for procedural sedation. Drugs 71:1481–1501
55. Muzyk AJ, Fowler JA, Norwood DK, Chilipko A (2011) Role of alpha2-agonists in the treatment of acute alcohol withdrawal. Ann Pharmacother 45:649–657
56. Driessen M, Lange W, Junghanns K, Wetterling T (2005) Proposal of a comprehensive clinical typology of alcohol withdrawal–a cluster analysis approach. Alcohol Alcohol 40:308–313
57. de Wit M, Best AM, Gennings C, Burnham EL, Moss M (2007) Alcohol use disorders increase the risk for mechanical ventilation in medical patients. Alcohol Clin Exp Res 31:1224–1230
58. Eyer F, Schuster T, Felgenhauer N, Pfab R, Strubel T, Saugel B, Zilker T (2011) Risk assessment of moderate to severe alcohol withdrawal–predictors for seizures and delirium tremens in the course of withdrawal. Alcohol Alcohol 46:427–433
59. Lukan JK, Reed DN Jr, Looney SW, Spain DA, Blondell RD (2002) Risk factors for delirium tremens in trauma patients. J Trauma 53:901–906
60. Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar). Br J Addict 1989;84:1353–7