Alcohol 86 (2020) 9–16

Contents lists available at ScienceDirect

Alcohol

journal homepage: http://www.alcoholjournal.org/

Alcohol-induced thrombocytopenia: Current review

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ARTICLE INFO

Article history:
Received 10 September 2019
Received in revised form
27 December 2019
Accepted 7 February 2020

Keywords:
Platelets
Thrombocytopenia
Predictors
Alcohol withdrawal syndrome
Delirium tremens

ABSTRACT

Thrombocytopenia is a decrease in the platelet count below 150,000 in a microliter of blood, i.e., below the lower limit of the reference range, which is 150,000–400,000/μL.

The phenomenon of thrombocytopenia related to heavy drinking began to arouse interest in the 1960s and 1970s. It was initially described in case reports and clinical studies on small groups. In the following years, the phenomenon itself and the significance of alcohol-induced thrombocytopenia was studied. Many methodological difficulties inhibiting objective conclusions from research were encountered. Model pathological mechanisms of alcohol thrombocytopenia and the effects of alcohol on the structure and function of platelets were described. Furthermore, the phenomenon of rapid normalization of the number of platelets in people who stopped drinking was described. Relationships between alcohol use, its intensity and occurrence, and intensity of thrombocytopenia have been demonstrated.

Predictive platelet counts for alcohol withdrawal syndrome complications have been proven and calculated. The risk of occurrence of withdrawal seizures or delirium tremens in alcohol withdrawal syndrome increases significantly when the platelet count is less than 119,000/μL.

The knowledge of the nature of the phenomenon of alcohol-induced thrombocytopenia in a clinical environment allows decisions that are more rational. The attention of clinicians should be drawn to the importance of results of blood tests routinely collected on admission.

Thrombocytopenia

There is strong evidence of alcohol use and its direct and indirect effects on bone marrow, even causing pancytopenia (Ballard, 1980; Girard, Kumar, & McAfee, 1987; Latvala, Parkkila, & Niemala, 2004; Manappallil, 2016; Nakao, Harada, Kondo, Mizushima, & Matsuda, 1991; Psaltopoulou et al., 2018). Thrombocytopenia is one of the hematological complications related to alcohol use that were studied for decades, and which may play an important role in diagnosis and management of alcohol use disorders (Silczuk, Habrat, & Lew-Starowicz, 2019).

Thrombocytopenia (TP) is a reduction in platelet counts (PLT) below 150,000 in a microliter of blood. The reference range is 150,000–400,000/μL. A significant reduction in the number of platelets (less than 50,000/μL) may favor the occurrence of petechiae. With extreme decreases (e.g., in TP due to immunological reasons, less than 1000/μL), there may be spontaneous (including intracranial) bleeding (Dembińska-Kieć & Naskalski, 2009; Kokot, Hyla-Klekot, & Kokot, 2011; Niemirowicz, Żelazowska-Rutkowska, Wysocka, & Car, 2012; Numminen, Hillbom, & Juvela, 1996; Rozenberg, 2011; Schneider & Krautzig, 2009; Wasiluk & Jasińska, 2010). The assessment of platelet function is based mainly on the results of a clinical examination. This examination consists of a detailed medical history together with an interview regarding the occurrence of similar symptoms and diseases in the family.

Primary (including hereditary) abnormalities in platelet number and/or platelet function are relatively rare. Most TP reasons are secondary to various causes. The result of pathophysiological changes in thrombocytes is mainly prolonged or excessive bleeding. Hence, bleeding time is one of the main tools in screening tests to assess platelet function (Ghoshal & Bhattacharyya, 2014). In developed countries, other assays are considered to be more specific and medically up to date. In 2015, Paniccia and colleagues reviewed contemporary platelet function tests, and delineated areas for future research development (Paniccia, Priora, Liotta, & Abbate, 2015).

The typical symptoms of thrombocyte dysfunction are:

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https://doi.org/10.1016/j.alcohol.2020.02.166

- ecchymosis of unknown origin or extensive bruising often associated with soft tissue hematomas
- epistaxis, in particular those that last for more than 30 min or cause anemia
- bleeding or spotting of the genital tract if they occur after menstruation
- bleeding of the gums
- heavy or prolonged bleeding after delivery
- bleeding after minor invasive procedures, such as tooth extraction, tonsillectomy, or appendectomy (Sharathkumar & Shapiro, 2008)

In cases of thrombocytopenia, clinicians should be aware that a low PLT does not protect against thrombosis; complications from thrombosis may be more dangerous than complications from bleeding (Balitsky & Arnold, 2018).

Drugs may induce alterations in platelet counts. Some drugs have a proven thrombocytogenic effect (PLT over 400,000−450,000/μL) on increasing the PLT (Frye & Thompson, 1993; Vo & Thompson, 2019). Almost any drug can change the number of platelets, and the pathological mechanism of drug-induced TP varies (George & Aster, 2009; Kenney & Stack, 2009; Sekhon & Roy, 2006; Visentin & Liu, 2007). Particular attention should be paid to TP caused by the drugs.

Alcohol and thrombocytopenia

Review of research

For the purposes of this study, literature on the occurrence of TP in drinkers of large amounts of alcohol was analyzed. Databases were searched (PubMed, Cochrane Library, Evidence Alerts, and Medscape) using various word search combinations: “alcohol”, “alcohol abuse”, “alcoholism”, “alcohol addiction”, “alcohol dependence”, “thrombocytopenia”, “platelets” “hematopoiesis”, and “bone marrow”.

Over 1500 articles from the 1950s to 2019 were obtained and analyzed for content. Items that related to other issues (e.g., drug-mediated thrombocytopenia) were rejected. It was only mentioned that alcohol could be one of the toxic agents for platelets. In contrast to the relatively large number of papers merely mentioning the relationship between TP and alcohol consumption, only a few studies go beyond duplicating the general claims about the alcohol-thrombocyte relationship. Attention is given to research results on this topic, but there is a lack of systematic review. Some of the articles refer to speculative hypotheses about the nature of alcohol-related thrombocytopenia, but they are not sufficiently supported by research. It is widely commented that the phenomenon of TP due to alcohol use is under-described and under-researched (Ballard, 1989, 1993, 1997; Lindenbaum, 1987; Lindenbaum & Hargrove, 1968; Straub, 1985).

Review of the accessible papers allowed them to be organized into thematic groups: the first reports; the prevalence of alcohol-related TP; platelet size and shape in alcohol TP; the dynamics of alcohol TP; pathological mechanisms of alcohol-related TP; the effects of alcohol on platelet function; complications of alcohol-related TP; TP as a prognostic factor in the development of complicated forms of AWS; and the management of alcohol-related TP.

The first reports

Knowledge about the adverse effects of alcohol on the morphology of blood components dates back to the first half of the 20th century. At that time, attention was paid mainly to alcohol-related megaloblastic anemia, which was associated with folic acid deficiencies. However, this mechanism has not been considered for the common thrombocytopenia associated with megaloblastic anemia. The phenomenon of rapidly appearing reticulocytosis and regressing TP began to be interpreted in terms of the disappearance of alcohol as a factor suppressing the formation of morphotic blood components (Jandl, 1955). The phenomenon of TP in relation to heavy drinking began to arouse interest in the 1960s and 1970s. It was described in cases of individual patients and later in small groups. It was experimentally shown that the phenomenon of TP has a different pathogenesis from the other alcohol-associated hematopoietic diseases (e.g., anemia caused by vitamin deficiency).

Over the next decades, clinical medicine was content with the general knowledge of TP caused by heavy alcohol drinking and the usually rapid normalization of PLT once heavy drinking stopped. In the meantime, knowledge about the physiology of thrombopoiesis, the pathophysiology of secondary TP (mainly drug-induced) and the relationships between various factors, as well as co-occurring processes that may affect the formation of thrombocytopenia, rapidly increased. However, this knowledge is scattered across various scientific journals addressed to diverse scientific branches (less often: clinicians). So far, no reliable consolidation has been undertaken in the form of a monograph or structured series of articles.

Sullivan and Herbert are considered to be the first to publish observations on the effect of alcohol on TP (Sullivan & Herbert, 1964). The authors described the cases of three patients consuming large amounts of alcohol and following a depleted diet. In those cases, these authors found changes in the morphotic composition of the blood typical for alcoholics, including TP. The research experiment aimed at explaining the role of alcohol suppressive effects and thiamine deficiency in patients. The effect of folic acid supplementation on the number of red blood cells is known. At a specific stage of the treatment, a diet rich in both folic acid and alcohol was administered. Two patients had a rapid regression of TP during alcohol withdrawal (AWS), and therefore the improvement was associated with AWS rather than folic acid supplementation.

Ten cases of hospitalization due to delirium tremens (DTs) were described in five alcohol-dependent subjects, and AWS was associated with rapid normalization of PLT. When subjects returned to heavy drinking, TP recurred (Lindenbaum & Hargrove, 1968). The same authors found that in the group of 43 “heavy alcoholics” at the beginning of hospitalization, TP below 100,000/μL occurred in 15 patients (34.9%). There were 20 patients (46.5%) whose PLT ranged between 100,000 and 150,000/μL. The results within the normal range (over 150,000/μL) were noted only in 8 people (18.6%) (Lindenbaum & Hargrove, 1968). Similar observations were made by other researchers who described 20 cases of TP (in some patients, recurrent), among whom eight persons were addicted to alcohol (Post & Desforges, 1968a).

The next two decades brought numerous case study reports of alcohol-related TP (Benmussa & Adnin, 1991; Hosseinnezhad, Vijayakrishnan, & Farmer, 2011; Jansen & Bieger, 1986; Koster, Wege, Ganzemuller, & Lengfelder, 2001; Ryback & Desforges, 1970; Zamir et al., 2004), along with review papers introducing this phenomenon to a wider medical audience (Alvarez-Sala Walther et al., 1979; Ballard, 1997; Cowan, 1975; Eichner, 1973; Erkurt, Kaya, Berber, Koroglu, & Kuku, 2012; Gauer & Braun, 2012; Gewirtz & Hoffman, 1986; Girard et al., 1987; Green & Trobridge, 1977; Guilarte Lopez-Manas, Callejas Rubio, Dominguez Vicent, & Ortego Centeno, 1996; Hanes, Quarles, & Boucher, 1997; Heidemann, Nerke, & Waller, 1981; Hillbom et al., 1985; Homann & Hasselbalch, 1992; Kiefel & Greinacher, 2010; Laso,

Celada, Diez-Jarilla, & Macias, 1979; Latvala, Parkkila, & Niemela, 2004; Levine, Spivak, Meagher, & Sieber, 1986; Littleton, Finn, Umney, & Yazdanbakhsh, 1982; Malik & Wickramasinghe, 1986; Mikhailidis, Jenkins, Barradas, Jeremy, & Dandona, 1986; Nakao et al., 1991; Numminen et al., 1996; Paraf, Coste, & Gouffier, 1971; Peltz, 1991; Rauchenzauner et al., 2005; Rubin & Rand, 1994; Ruf, 2004; Sahud, 1972; Scharf & Aul, 1988; Schmidt, 1983; Smith, Tobin, Burris, & White, 1992; Soegaard & Ingeberg, 1985; Stobbe, 1981; Straub, 1985; Wilson, 1980).

The prevalence of alcohol-related thrombocytopenia

Due to methodological difficulties, there are few studies on the incidence of all types of TP (Galdarossa et al., 2012). Apart from cases of isolated, primary TP (idiopathic is one of the most frequent diagnoses) without other co-existing symptoms and disorders, research on the prevalence of secondary thrombocytopenia is difficult. The reason given for these difficulties is the omission of TP as a diagnosis, while it is common to regard thrombocytopenia as one of the symptoms (e.g., in the case of pancytopenia). TP is also definitively diagnosed only when found using laboratory tests (e.g., when focusing on serious complications due to coagulation disorders).

The assessment of the prevalence of TP among alcohol users or addicts is based mainly on studies performed on small groups, with fewer than 100 subjects (Lindenbaum & Hargrove, 1968; Post & Desforges, 1968b). Typically, “epidemiological” data come from studies on special populations. The focus is on the populations of people locally hospitalized due to severe AWS (often complicated) who have been found to have abnormalities in routine blood counts (Berggren, Fahlke, & Balldin, 2000; Kim et al., 2015; Lindenbaum & Hargrove, 1968; Post & Desforges, 1968b). Much less data and less structured research comes from other clinical departments (e.g., internal medicine, hematology, neurosurgery), where an alcohol history study was screened for the causes of thrombocytopenia (Latvala et al., 2004; Sheikh et al., 2012; Stephan, Montblanc, Cheffi, & Bonnet, 1999). Studies are difficult to compare due to the adoption of various different diagnostic criteria. Often, the studied populations are generally called “alcoholics”, sometimes with the adjectives “chronic”, “heavy”, which do not correspond to official classifications, and without providing accepted diagnostic criteria. Sometimes study groups are described by the terms “a lot of drinkers”, “alcohol abusers”, etc. Most of the papers on alcohol-related TP concern people hospitalized for severe AWS (Berggren et al., 2009), often complicated by DTs and/or withdrawal seizures (wS) (Berggren et al., 2009; Kim et al., 2015).

There are no major discrepancies with regard to the accepted criteria for TP, because the cut-off point for diagnosis is commonly assumed to be below 150,000/μL. In some studies, TP is split depending on the degree of thrombocytopenia (e.g., by dividing it into subgroups, with a different division every 50,000/μL) (Lindenbaum & Hargrove, 1968). However, morbidly increased TP and its consequences in the form of complications (such as bleeding, hemorrhaging) in this group of people are rare and are rather not considered to be life-threatening conditions (Baumgartner et al., 1988; Cantor & Orkin, 2002; Dembińska-Kieć & Naskalski, 2009; Handin, Lux, & Stossel, 2003; Hillbom, 1998; Ishii et al., 2011; Kim et al., 2015; Kokot et al., 2011; Lustenberger et al., 2011; Niemirowicz et al., 2012; Numminen et al., 1996; Peltz, 1991; Schneider & Krautzig, 2009; Rozenberg, 2011; Wasiluk & Jasińska, 2010). If bleeding appears, other causes should always be considered (Curnow, Pasalic, & Favaloro, 2016). For example, among alcoholic patients, coagulation disorders may be secondary to, for example, liver cirrhosis, gastritis and gastric ulcers, or hypertension (Strate et al., 2016).

For these methodological reasons, the prevalence of TP is described and assessed in a wide range: from 3% to 43% of healthy, well-fed people addicted to alcohol and from 14% to 81% of alcohol-dependent patients requiring hospitalization (Ballard, 1997). TP may occur on average in every fourth hospitalized alcohol-dependent patient (Handin et al., 2003).

The dynamics of alcohol thrombocytopenia

The observed phenomenon of thrombocytopenia associated with the use of alcohol is generally a quickly transient condition. PLT usually stabilizes about a week after alcohol cessation, returning to or exceeding the normal range (Lindenbaum & Hargrove, 1968; Mikhailidis et al., 1986; Peltz, 1991; Stobbe, 1981; Straub, 1985).

This phenomenon is explained by the fact that about 1/3 of all platelets are stored in the spleen. The administration of noradrenaline (Bakovic et al., 2013) or sensory stimulation of the sympathetic system (Chen et al., 2016) causes platelet release into the bloodstream. Thus, the phenomenon of noradrenergic hyperactivity in alcohol withdrawal syndrome can be an important factor in the dynamics of platelet release from the spleen reservoir into the bloodstream. People addicted to alcohol often present poor compliance with doctors and researchers. For this reason, there is a lack of research involving long-term observation of PLT, and even less of its function. There are few known descriptions of people who had rapid normalization of PLT during short-term hospitalization. After discharge from the hospital, patients returned to compulsive drinking of alcohol; in the case of subsequent hospitalization, they also had recurrent TP (Lindenbaum & Hargrove, 1968). In case of alcohol-induced TP appearance, the number of days until ‘normalization’ was similar in groups of complicated and non-complicated AWS (Silczuk et al., 2019).

Platelet size and shape in alcohol thrombocytopenia

Only a few studies assess not only the number of thrombocytes, but also their size. Alcohol has been shown to change the proportion of platelets in the bloodstream in humans; also, there is a relative increase in PLT of larger size and weight (which is considered younger) relative to the number of smaller and lighter ones (Sahud, 1972). This is probably due to the compensatory mechanism of platelet release from spleen storage in the event of toxic platelet damage in circulating blood. One of these mechanisms is the stimulation of the sympathetic nervous system (Bakovic et al., 2013; Chen et al., 2016). An experiment was performed on guinea pigs that were given alcohol at doses “comparable to moderate amounts in humans”, and its effect was found to be not only on the PLT, but also on their size, and to produce deformation of megakaryocytes (Smith et al., 1992).

Pathological mechanisms of alcohol thrombocytopenia

The pathogenesis of alcohol-related thrombocytopenia is not satisfactorily understood and is likely to be complex. Already in the first studies from the 1960s and 1970s, it was pointed out that the reduction in the PLT in alcohol users may have a different origin than in the case of megaloblastic anemia, where folic acid deficiency, liver damage, and reduced iron ions play an important role.

In alcohol-related thrombocytopenia, platelet toxicity was directly suspected, with at least two mechanisms already suspected: myelosuppression and platelets in the bloodstream (Post & Desforges, 1968a). Indirect evidence of alcohol effects was obtained by demonstrating:

- rapid normalization of PLT after cessation of drinking (Cowan & Hines, 1971) and rapid recurrence of TP in the event of recurrence of heavy drinking
- no effect of corticosteroid administration (Lindenbaum & Hargrove, 1968)
- no relationship between the severity of thrombocytopenia and the degree of liver damage
- vitamin deficiencies (especially folic acid), and massive bleeding (Lindenbaum & Hargrove, 1968)

Studies were done that included oral administration of alcoholic beverages to patients (Sullivan & Herbert, 1964) and intravenous administration of a 5% alcohol solution (Post & Desforges, 1968b). In the latter case, a reduction in PLT was observed as early as 4–6 h after alcohol infusion. However, the mechanism of these changes remained unknown. The following were taken into account: the effect of alcohol-induced changes in catecholamine and serotonin metabolism, and the effect on cortisol levels that have the property of increasing aggregation and platelet destruction (Post & Desforges, 1968a). It is believed that alcohol affects the production of thrombocytes and accelerates their degradation, although most researchers usually focus on only one element of pathogenesis. It is believed that the course of TP of a non-alcoholic etiology is chronic, and a greater role is played by immunological mechanisms.

In the case of alcohol-related TP, factors of direct alcohol toxicity to the thrombogenesis system dominate, and the disappearance of the toxic factor restores natural physiological processes (Ballard, 1997; Cantor & Orkin, 2002). Alcohol has been shown to pathomorphologically cause bone marrow changes, and this also applies to thrombopoiesis (Latvala et al., 2004; Post & Desforges, 1968a). The mechanism of this toxicity is not sufficiently understood and explained. Recently, it has been hypothesized that people with some variants of aldehyde dehydrogenase may have increased levels of acetaldehyde (Yokoyama et al., 2017), which can damage DNA in bone marrow cells (Smith et al., 2015). The thesis about individual susceptibility to alcohol is supported by a previous case report of a patient with TP responding to relapses of drinking of alcohol. In this case, it has been shown that the growth of the myonuclear mononuclear cell colony was inhibited in response to significantly lower alcohol concentrations than was the case with cell colonies taken from healthy volunteers (Nakao et al., 1991).

Although several studies have shown that thrombocytopenia can occur independently of liver damage (Lindenbaum & Lieber, 1969; Post & Desforges, 1968a), other publications have shown that liver damage, especially cirrhosis, plays an important role in the pathogenesis of TP of various etiologies (Mitchell, Feldman, Diakow, & Sigal, 2016; Peck-Radosavljevic, 2017). Until recently, the dominant belief was that the main mechanism of TP in people with liver damage is increased portal pressure leading to splenomegaly. The enlarged spleen accelerates the destruction of blood morphotic elements, mainly platelets. This hypothesis raised growing doubts when it was discovered that procedures to restore physiological portal pressure do not reduce TP. In recent years, researchers have favored the hypothesis that in the case of cirrhosis or other liver damage, the reduced hepatocyte mass produces smaller amounts of thrombopoietin that stimulates the bone marrow to produce thrombocytes (Peck-Radosavljevic, 2016).

The complementary hypothesis is that alcohol (or its metabolites) exerts the toxic effects on mature thrombocytes that are already in the blood. This was confirmed by experimental animal studies (Malik & Wickramasinghe, 1986). The toxic effect of alcohol on platelets was experimentally confirmed in an alcohol-dependent patient who was administered intravenous ethanol solutions. It was discovered that a reduction in PLT of up to 40% occurred after 5–7 h (Post & Desforges, 1968b). A similar immediate effect of direct toxicity was observed in other studies (Sullivan & Herbert, 1964; Sullivan, Liu, & Talarico, 1968).

Another not quite competitive, but complementary, concept concerns the possibility that alcohol accelerates platelets apoptosis (Liu et al., 2017). In earlier literature, moderate effects of alcohol on platelet life expectancy and the formation of adverse ultrastructural changes in their structure were signaled (Ballard, 1997; Cantor & Orkin, 2002). It is well known that ethanol is a pro-apoptotic factor in nucleated cells, e.g., some fibroblasts or hepatocytes (Chen et al., 2011; Higuchi, Kurose, Kato, Miura, & Ishii, 1996). In the platelets, such a mechanism was suspected. There was no scientific evidence to confirm this hypothesis. Recently, one work based on the *in vitro* model and mouse studies showed the mechanism of internal mitochondrial platelet apoptosis is due to chronic use of ethanol (Liu et al., 2017); internal mitochondrial platelet apoptosis is considered the basic apoptotic mechanism of thrombocytes (Wang et al., 2017; Zhang, Das, Siddiqui, & Myers, 2000). In the 1970s, a hypothesis was formulated about the causative role of hyperosmolality in the development of TP (Cowan, Graham, & Shook, 1976), but this issue was never studied later.

In summary, TP that occurs in heavy drinkers traditionally is classified as secondary TP, which is an effect of alcohol toxicity. It can be presumed that this phenomenon is more complex. In the pathogenesis of TP, there is an interaction of the toxic effects of alcohol with some increased susceptibility, which is probably genetically determined.

Effects of alcohol on platelet function

In addition to affecting the size of platelets and causing TP, alcohol usually has a negative effect on platelet function. In particular, this applies to coagulation disorders. PLT decreases and probably alters platelet coagulation activity (Ehrlich & Humpel, 2014). People with alcohol-related TP usually have longer bleeding times, which decrease as PLT normalizes.

The risk of major bleeding increases with a dysfunction of other coagulation factors, whose production is impaired by frequent liver damage and other hepatotoxic factors in alcohol dependence. However, the increased risk of major bleeding seems uncommon due to the rapid resolution of TP and related coagulation disorders. Some increased risk of post-traumatic bleeding in alcohol addicts is reported (Shen, Gao, Lee, & Nan, 2018). Drinking alcohol and its effect on the coagulation system may be one of the factors reducing the risk of cardiovascular incidents in people following the so-called Mediterranean diet, in which moderate, although systematic, alcohol consumption is typical (Zhang et al., 2000). On the other hand, administration of alcohol to healthy volunteers has been shown to increase thrombocyte aggregation. In alcohol addicts, platelet aggregation associated with thromboxane B2 increases 4-fold (Hillbom et al., 1985). In addition, platelets play many other physiological functions that can be disrupted by alcohol. This applies to, among other factors, to the influence of alcohol on immune responses (Gill, Jindal, Jagdis, & Vadas, 2015). For example, there are enzymes that metabolize neurotransmitters in platelets, including monoamine oxidase. It cannot be ruled out that the effect of alcohol on platelets may result in a change in the amount and/or activity of monoamine oxidases, which in turn may contribute to imbalances of neurotransmitters that result in the development of psychotic disorders, e.g., mood disorders, anxiety disorders, or DTs (Berggren et al., 2000; Takahashi, Tani, & Yamane, 1976). A similar phenomenon concerns the serotoninergic system (Llinás et al., 2014). To confirm this hypothesis, however, requires in-depth research. *In vitro* studies have not shown that alcohol affects the synthesis of platelet prostaglandins (Stuart, 1979).

Recently, attention has also been paid to a specific role of platelets in creating a protective blood–brain barrier. In a situation where platelet-damaging factors occur not individually, but jointly (e.g., alcohol + HIV infection), there is an increased risk of damaging the blood–brain barrier, thereby causing subsequent damage to brain structures as well as cognitive impairment (Nair, Maria, Agudelo, Yndart, & Vargas-Rivera, 2015). The effect of alcohol use disorders on PECAM-1 (Platelet Endothelial Cell Adhesion Molecule-1) and on oligodendrogenesis has been demonstrated (Mandyam et al., 2017). Alcohol may negatively affect myelination of nerve fibers and the ability to learn and adapt to environmental changes. Additionally, other studies have shown that not one, but several, pathogenic factors act in clinical situations, e.g., in addition to alcohol exposure, such as liver damage, including cirrhosis of various etiologies, HCV and/or HIV infections, co-occurrence of cocaine use, etc. (Hosseinnezhad et al., 2011). This multifactorial aspect remains poorly understood.

Complications of alcoholic thrombocytopenia

Most frequently, early remission of alcohol TP usually proceeds without serious complications (Peltz, 1991). However, bleeding can occur, from simple nosebleeds to intracerebral hematomas (Ballard, 1997).

Cases of serious intracranial bleeding associated with alcohol-related TP are rare (Baumgartner et al., 1988; Dembińska-Kieć & Naskalski, 2009; Hillbom, 1998; Ishii et al., 2011; Kokot et al., 2012; Niemirowicz et al., 2012; Numminen et al., 1996; Rozenberg, 2011; Schneider & Krautzig, 2009; Wasiluk & Jasińska, 2010).

Thrombocytopenia as a prognostic factor in the development of complicated forms of alcohol withdrawal syndrome

Alcohol withdrawal (AWS) may have life-threatening complications, such as DTs and wS. The ability to predict the transition of uncomplicated AWS into complicated forms may play the key role in preventing those complications by using treatment that is more aggressive in hospital conditions (Lee et al., 2005; Saitz et al., 1994). There are factors commonly regarded as prognostic, such as the occurrence of complicated forms in the past, the dynamics consisting of the exacerbation of already intensified AWS, the taking of sedatives and sleeping pills, tachycardia, etc. (Kraemer, Mayo-Smith, & Calkins, 2003; Lee et al., 2005; Mayo-Smith & Bernard, 1995). In recent years, among parameters used to assess the risk of complicated AWS, evidence for TP has grown (Berggren et al., 2009; Eyer et al., 2011; Goodson, Clark, & Douglas, 2014; Huang et al., 2011; Kim et al., 2015; Monte, Rabunal, Casariego, Bal, & Pertega, 2009).

For the first time, the potential predictive value of TP was noticed in studies on a small number of people (Berggren et al., 2000). Then, the same authors added TP to the list of other more known predictive factors. They found that TP is more common in people who developed either DTs or wS. It was found that in the case of DTs, predictive TP had 70% sensitivity and specificity 70%, while positive predictive value was 6% and negative predictive value was 99%. In the event of wS, these parameters were 75%, 69%, 6%, and 99%, respectively (Berggren et al., 2009). The authors emphasized that relationships between these parameters are not known, and it is possible that they are parallel phenomena caused by another factor, in this case the toxic effects of alcohol. However, a certain causal relationship cannot be excluded, as it has been discovered that alcohol can affect not only PLT itself, but also some of their functions, e.g., monoamine oxidase activity, which may result in the development of psychotic symptoms (Berggren et al., 2000; Takahashi et al., 1976). A similar paper was published two years later. Among other factors that were selected as potential predictors, PLT was also studied, and a lower PLT was found to be predictive of DTs (Eyer et al., 2011).

In comparative studies of patients hospitalized due to uncomplicated AWS and AWS complicated by DTs, it was shown that among the analyzed laboratory tests, only a smaller PLT ($p = 0.007$) and the Prothrombin Ratio (Quick Index) ($p = 0.03$) differed in both groups (Monte et al., 2009). During the research on the role of BDNF concentration in the pathogenesis of DTs, it was found that the group in which there was progression from uncomplicated AWS to DTs had an average lower PLT than in the group in which DTs did not develop. However, this difference was not statistically significant (Huang et al., 2011). A meta-analysis of data was performed, which aimed to organize knowledge on prognostic factors of the transition of uncomplicated AWS into complicated forms (Goodson et al., 2014). From among 225 papers on this topic, 15 that were methodologically correct were selected and entered the meta-analysis. Among the 117 variables studied, the PLT was one of the parameters assessed in four studies (Berggren et al., 2009; Eyer et al., 2011; Huang et al., 2011; Monte et al., 2009). These studies included 1527 patients; in 227 (14.9%) cases, DTs developed. TP has been shown to differ between these groups at $p = 0.003$. A similar, though less significant, regularity ($p = 0.01$) was demonstrated in two studies (Berggren et al., 2009; Eyer et al., 2011) involving 1160 patients with uncomplicated AWS, among whom wS occurred in 69 people (n = 5; 9%). The most important conclusion of this meta-analysis was that only two of the studied parameters have a predictive value; these parameters are the occurrence of complicated AWS in the past and the present occurrence of TP (Goodson et al., 2014).

Recently, it has been shown that lower PLT combined with high homocysteine levels is associated with an increased likelihood of developing DTs (Kim et al., 2015). In contrast, in people with wS, TP

Table 1
Alcohol-induced thrombocytopenia.

Prevalence	TP occurs in: • 3%–43% of healthy, well-fed alcohol-dependent people • 14%–81% of alcohol-dependent patients who require hospitalization • 25% of hospitalized alcohol-dependent patients
Pathological mechanism	• alcohol affects the production of thrombocytes • alcohol accelerates degradation and apoptosis of platelets
Dynamics	• PLT usually stabilizes about a week after alcohol cessation
Complications	• usually without serious complications • bleeding can occur, from simple nosebleeds to intracerebral hematomas
Thrombocytopenia in alcohol withdrawal	• PLT predicts AWS severity • PLT <119,000/μL predicts AWS complications (seizures, delirium)
Management	• depends on the degree of thrombocytopenia • every patient with TP should be monitored after cessation of alcohol use

has already proven to be an independent risk factor for the development of DTs (Kim et al., 2015). However, the authors do not exclude that the possibility of reduced PLT and the occurrence of DTs may be phenomena accompanying heavy drinking. The relationship between the occurrence of TP and AWS was finally studied in a population of 300 patients. Groups of people with complicated (n = 150) and uncomplicated alcohol withdrawal syndrome (n = 150) were compared in terms of PLT. Special attention in constructing the research project was directed to methodological correctness and detailed exclusion criteria. It has been found that TP is significantly more common in hospitalized patients with AWS with complications rather than in hospitalized patients without complications. The risk of seizure or DTs increases significantly when PLT is less than 119,000/μL (Silczuk et al., 2019).

Management of alcohol-related thrombocytopenia

Management of alcohol-related TP depends on the degree of TP. The incidence of the bleeding may force a need for antiplatelet agents and anticoagulation. With mild to moderate TP, the extensive evaluation may not be necessary. Monitoring of every case of TP after cessation of alcohol use is appropriate.

In the case of diagnosed alcohol-related TP, more importance is attached to the prevention of possible complications rather than to the treatment itself. This prophylaxis is based on the principles of management in cases of TP with non-alcoholic causes. It involves, among others, avoiding the use of non-steroidal anti-inflammatory drugs, including salicylates. Others include gentle and regular care for dental and periodontal hygiene, hormonal therapy for menstrual disorders, and careful planning of surgical procedures. In cases of vaginal or nasal bleeding, tamponades with the addition of thrombin are used (Sharathkumar & Shapiro, 2008). The prolonged bleeding time described in *in vivo* studies, and delayed coagulation in alcohol intoxication, may result in gastrointestinal hemorrhage, among other conditions. This will require an individualized diagnostic and therapeutic approach, ensuring the possibility of specialist intervention (e.g., surgical or hematological).

In the available literature, neither the test results nor the recommendations to people with alcohol-related TP were found. It is generally thought that alcohol discontinuation is sufficient. In one paper, such conduct falls within the proposed standards for the treatment of TP (Gauer & Braun, 2012).

Summary

The phenomenon of TP in alcohol users and alcohol-dependent patients, despite being studied for decades, still leaves many interesting research hypotheses. A schematic summary is presented in Table 1. Following the evolution of publications, one can see a set of cognitive values arising from the interest in the phenomenon to obtain practical information on clinical use. In the light of recent studies, the prognostic value of PLT for prognosis of complications of AWS is noteworthy. It may be the starting point for further in-depth clinical studies on increasing the effectiveness of treatment of alcohol dependence and its complications. In addition, the knowledge of the nature of the phenomenon of alcohol TP allows physicians to make more rational decisions (e.g., avoiding transfusions of platelet preparations, glicocorticotherapy), except for special cases (bleeding, risk of hemorrhagic stroke, urgent surgeries). The direct clinical benefit resulting from the conclusions of this paper is to draw the attention of clinicians to the importance of results of blood tests routinely collected on admission, and when TP with or without associated hypokalemia is diagnosed among them, to provide greater care and attention to AWS patients.

References

Alvarez-Sala Walther, J. L., Urban Poza, M. A., Sicilia de Salamanca, J. J., Fernandez Mendieta, F., Serrano Heranz, R., & Espinos Perez, D. (1979). [Hematologic aspects of alcoholism (author's transl)]. *Medicina Clínica, 72*, 158–165.

Bakovic, D., Pivac, N., Eterovic, D., Breskovic, T., Zubin, P., Obad, A., et al. (2013). The effects of low-dose epinephrine infusion on spleen size, central and hepatic circulation and circulating platelets. *Clinical Physiology and Functional Imaging, 33*, 30–37. https://doi.org/10.1111/j.1475-097X.2012.01156.x.

Balitsky, A., & Arnold, D. (2018). The use of anticoagulation in patients with thrombocytopenia. *Hematologist, 15*, 5.

Ballard, H. S. (1980). Alcohol-associated pancytopenia with hypocellular bone marrow. *American Journal of Clinical Pathology, 73*, 830–834. https://doi.org/10.1093/ajcp/73.6.830.

Ballard, H. S. (1989). Hematological complications of alcoholism. *Alcoholism: Clinical and Experimental Research, 13*, 706–720. https://doi.org/10.1111/j.1530-0277.1989.tb00408.x.

Ballard, H. S. (1993). Alcohol, bone marrow, and blood. *Alcohol Health & Research World, 17*, 310–315.

Ballard, H. S. (1997). The hematological complications of alcoholism. *Alcohol Health & Research World, 21*, 42–52.

Baumgartner, C., Zeiler, K., Auff, E., Dal Bianco, P., Holzner, F., Lesch, O. M., et al. (1988). [Does alcohol consumption promote the manifestation of strokes? Considerations on pathophysiology]. *Wiener Klinische Wochenschrift, 100*, 99–107.

Benmussa, P., & Adnin, F. (1991). [Thrombocytopenia in acute alcohol intoxication]. *Presse Medicale, 20*, 1457–1458.

Berggren, U., Fahlke, C., & Balldin, J. (2000). Transient increase in platelet monoamine oxidase b activity during early abstinence in alcoholics: Implications for research. *Alcohol and Alcoholism, 35*, 377–380. https://doi.org/10.1093/alcalc/35.4.377.

Berggren, U., Fahlke, C., Berglund, K. J., Blennow, K., Zetterberg, H., & Balldin, J. (2009). Thrombocytopenia in early alcohol withdrawal is associated with development of delirium tremens or seizures. *Alcohol and Alcoholism, 44*, 382–386. https://doi.org/10.1093/alcalc/agp012.

Cantor, A. B., & Orkin, S. H. (2002). Transcriptional regulation of erythropoiesis: An affair involving multiple partners. *Oncogene, 21*, 3368–3376. https://doi.org/10.1038/sj.onc.1205326.

Chen, S., Du, C., Shen, M., Zhao, G., Xu, Y., Yang, K., et al. (2016). Sympathetic stimulation facilitates thrombopoiesis by promoting megakaryocyte adhesion, migration, and proplatelet formation. *Blood, 127*, 1024–1035. https://doi.org/10.1182/blood-2015-07-660746.

Chen, C. C., Liou, S. W., Chen, C. C., Chen, W. C., Hu, F. R., Wang, I. J., et al. (2011). Coenzyme Q10 reduces ethanol-induced apoptosis in corneal fibroblasts. *PloS One, 6*, e19111. https://doi.org/10.1371/journal.pone.0019111.

Cowan, D. H. (1975). The platelet defect in alcoholism. *Annals of the New York Academy of Sciences, 252*, 328–341. https://doi.org/10.1111/j.1749-6632.1975.tb19175.x.

Cowan, D. H., Graham, R. C., Jr., & Shook, P. (1976). Hyperosmolality: A factor in ethanol-related platelet dysfunction? *Seminars in Hematology, 13*, 103–114.

Cowan, D. H., & Hines, J. D. (1971). Thrombocytopenia of severe alcoholism. *Annals of Internal Medicine, 74*, 37–43. https://doi.org/10.7326/0003-4819-74-1-37.

Curnow, J., Pasalic, L., & Favaloro, E. J. (2016). Why do patients bleed? *Surgery Journal, 2*, e29–e43. https://doi.org/10.1055/s-0036-1579657.

Dembińska-Kieć, A., & Naskalski, J. W. (2009). *Diagnostyka laboratoryjna z elementami biochemii klinicznej*. Wrocław: Urban & Partner.

Ehrlich, D., & Humpel, C. (2014). Effects of ethanol on aggregation, serotonin release, and amyloid precursor protein processing in rat and human platelets. *Platelets, 25*, 16–22. https://doi.org/10.3109/09537104.2013.764979.

Eichner, E. R. (1973). The hematologic disorders of alcoholism. *The American Journal of Medicine, 54*, 621–630. https://doi.org/10.1016/0002-9343(73)90120-4.

Erkurt, M. A., Kaya, E., Berber, I., Koroglu, M., & Kuku, I. (2012). Thrombocytopenia in adults: Review article. *Journal of Hematology, 1*, 44–53.

Eyer, F., Schreckenberg, M., Hecht, D., Adorjan, K., Schuster, T., Felgenhauer, N., et al. (2011). Carbamazepine and valproate as adjuncts in the treatment of alcohol withdrawal syndrome: A retrospective cohort study. *Alcohol and Alcoholism, 46*, 177–184. https://doi.org/10.1093/alcalc/agr005.

Frye, J. L., & Thompson, D. F. (1993). Drug-induced thrombocytosis. *Journal of Clinical Pharmacy and Therapeutics, 18*, 45–48. https://doi.org/10.1111/j.1365-2710.1993.tb00565.x.

Galdarossa, M., Vianello, F., Tezza, F., Allemand, E., Treleani, M., Scarparo, P., et al. (2012). Epidemiology of primary and secondary thrombocytopenia: First analysis of an administrative database in a major Italian institution. *Blood Coagulation and Fibrinolysis, 23*, 271–277. https://doi.org/10.1097/MBC.0b013e328351882d.

Gauer, R. L., & Braun, M. M. (2012). Thrombocytopenia. *American Family Physician, 85*, 612–622.

George, J. N., & Aster, R. H. (2009). Drug-induced thrombocytopenia: Pathogenesis, evaluation, and management. *Hematology*, 153–158. https://doi.org/10.1182/asheducation-2009.1.153. American Society of Hematology. Education Program.

Gewirtz, A. M., & Hoffman, R. (1986). Transitory hypomegakaryocytic thrombocytopenia: Aetiological association with ethanol abuse and implications regarding regulation of human megakaryocytopoiesis. *British Journal of Haemotology, 62*, 333–344. https://doi.org/10.1111/j.1365-2141.1986.tb02937.x.

Ghoshal, K., & Bhattacharyya, M. (2014). Overview of platelet physiology: Its hemostatic and nonhemostatic role in disease pathogenesis. *ScientificWorldJournal, 2014*, 781857. https://doi.org/10.1155/2014/781857.

Gill, P., Jindal, N. L., Jagdis, A., & Vadas, P. (2015). Platelets in the immune response: Revisiting platelet-activating factor in anaphylaxis. *The Journal of Allergy and Clinical Immunology, 135*, 1424–1432. https://doi.org/10.1016/j.jaci.2015.04.019.

Girard, D. E., Kumar, K. L., & McAfee, J. H. (1987). Hematologic effects of acute and chronic alcohol abuse. *Hematology-Oncology Clinics of North America, 1*, 321–334.

Goodson, C. M., Clark, B. J., & Douglas, I. S. (2014). Predictors of severe alcohol withdrawal syndrome: A systematic review and meta-analysis. *Alcoholism: Clinical and Experimental Research, 38*, 2664–2677. https://doi.org/10.1111/acer.12529.

Green, J. B., 3rd, & Trobridge, A. A. (1977). Hematologic and oncologic implications of alcoholism. *Postgraduate Medicine, 61*, 149–154. https://doi.org/10.1080/00325481.1977.11712191.

Guilarte Lopez-Manas, J., Callejas Rubio, J. L., Dominguez Vicent, J. R., & Ortego Centeno, N. (1996). [Reversible thrombopenia caused by alcohol. A condition to consider]. *Anales de Medicina Interna, 13*, 354.

Handin, R. I., Lux, S. E., & Stossel, T. P. (2003). *Blood: Principles and practice of Hematology*. Philadelphia: Lippincott Williams & Wilson.

Hanes, S. D., Quarles, D. A., & Boucher, B. A. (1997). Incidence and risk factors of thrombocytopenia in critically ill trauma patients. *The Annals of Pharmacotherapy, 31*, 285–289. https://doi.org/10.1177/106002809703100302.

Heidemann, E., Nerke, O., & Waller, H. D. (1981). [Alcohol induced changes in hemopoiesis (author's transl)]. *Klinische Wochenschrift, 59*, 1303–1312. https://doi.org/10.1007/bf01711180.

Higuchi, H., Kurose, I., Kato, S., Miura, S., & Ishii, H. (1996). Ethanol-induced apoptosis and oxidative stress in hepatocytes. *Alcoholism: Clinical and Experimental Research, 20*, 340a–346a.

Hillbom, M. (1998). Alcohol consumption and stroke: Benefits and risks. *Alcoholism: Clinical and Experimental Research, 22*, 352s–358s. https://doi.org/10.1097/00000374-199807001-00012.

Hillbom, M., Kangasaho, M., Lowbeer, C., Kaste, M., Muuronen, A., & Numminen, H. (1985). Effects of ethanol on platelet function. *Alcohol, 2*, 429–432. https://doi.org/10.1016/0741-8329(85)90109-0.

Homann, C., & Hasselbalch, H. C. (1992). Hematological abnormalities in alcoholism. *Ugeskrift for Lager, 154*, 2184–2187.

Hosseinnezhad, A., Vijayakrishnan, R., & Farmer, M. J. (2011). Acute renal failure, thrombocytopenia, and elevated liver enzymes after concurrent abuse of alcohol and cocaine. *Clinics and Practice, 1*, e35. https://doi.org/10.4081/cp.2011.e35.

Huang, M. C., Chen, C. H., Liu, H. C., Chen, C. C., Ho, C. C., & Leu, S. J. (2011). Differential patterns of serum brain-derived neurotrophic factor levels in alcoholic patients with and without delirium tremens during acute withdrawal. *Alcoholism: Clinical and Experimental Research, 35*, 126–131. https://doi.org/10.1111/j.1530-0277.2010.01329.x.

Ishii, Y., Harada, K., Kuroda, R., Nagai, H., Nakajima, M., Saito, N., et al. (2011). Bilateral thalamic haemorrhage and intracranial injuries related to alcohol-induced thrombocytopenia. *Journal of Clinical Pathology, 64*, 1034–1035. https://doi.org/10.1136/jclinpath-2011-200023.

Jandl, J. H. (1955). The anemia of liver disease: Observations on its mechanism. *Journal of Clinical Investigation, 34*, 390–404. https://doi.org/10.1172/jci103087.

Jansen, E. H., & Bieger, R. (1986). [Severe thrombocytopenia due to alcohol abuse]. *Nederlands Tijdschfift Voor Geneeskunde, 130*, 1612–1614.

Kenney, B., & Stack, G. (2009). Drug-induced thrombocytopenia. *Archives of Pathology & Laboratory Medicine, 133*, 309–314. https://doi.org/10.1043/1543-2165-133.2.309.

Kiefel, V., & Greinacher, A. (2010). [Differential diagnosis and treatment of thrombocytopenia]. *Internist (Berl), 51*, 1397–1410. https://doi.org/10.1007/s00108-010-2731-1.

Kim, S. H., Lee, J. H., Joo, W., Chough, C. K., Park, H. K., Lee, K. J., et al. (2015). Analysis of the risk factors for development of post-operative extradural hematoma after intracranial surgery. *British Journal of Neurosurgery, 29*, 243–248. https://doi.org/10.3109/02688697.2014.967749.

Kokot, F., Hyla-Klekot, L., & Kokot, S. (2011). *Badania Laboratoryjne. Zakres Norm I Interpretacja*. Warsaw: PZWL.

Koster, M., Wege, T., Ganzemuller, C., & Lengfelder, W. (2001). [44-year-old patient with thrombocytopenia, multiple organ failure and disseminated intravascular coagulation caused by drug poisoning with paracetamol, metamizole, benzodiazepines and alcohol in attempted suicide]. *Internist (Berl), 42*, 905–909. https://doi.org/10.1007/s001080170134.

Kraemer, K. L., Mayo-Smith, M. F., & Calkins, D. R. (2003). Independent clinical correlates of severe alcohol withdrawal. *Substance Abuse, 24*, 197–209. https://doi.org/10.1023/a:1026099426602.

Laso, F. J., Celada, A., Diez-Jarilla, J. L., & Macias, J. G. (1979). [The hematologic disorders of alcoholism (author's transl)]. *Schweizerische Rundschau fur Medizin Praxis, 68*, 1111–1117.

Latvala, J., Parkkila, S., & Niemela, O. (2004). Excess alcohol consumption is common in patients with cytopenia: Studies in blood and bone marrow cells. *Alcoholism: Clinical and Experimental Research, 28*, 619–624. https://doi.org/10.1097/01.alc.0000122766.54544.3b.

Lee, J. H., Jang, M. K., Lee, J. Y., Kim, S. M., Kim, K. H., Park, J. Y., et al. (2005). Clinical predictors for delirium tremens in alcohol dependence. *Journal of Gastroenterology and Hepatology, 20*, 1833–1837. https://doi.org/10.1111/j.1440-1746.2005.03932.x.

Levine, R. F., Spivak, J. L., Meagher, R. C., & Sieber, F. (1986). Effect of ethanol on thrombocytopoiesis. *British Journal of Haematology, 82*, 345–354. https://doi.org/10.1111/j.1365-2141.1986.tb02938.x.

Lindenbaum, J. (1987). Hematologic complications of alcohol abuse. *Seminars in Liver Disease, 7*, 169–181. https://doi.org/10.1055/s-2008-1040574.

Lindenbaum, J., & Hargrove, R. L. (1968). Thrombocytopenia in alcoholics. *Annals of Internal Medicine, 68*, 526–532. https://doi.org/10.7326/0003-4819-68-3-526.

Lindenbaum, J., & Lieber, C. S. (1969). Hematologic effects of alcohol in man in the absence of nutritional deficiency. *New England Journal of Medicine, 281*, 333–338. https://doi.org/10.1056/NEJM196908142810701.

Littleton, J. M., Fenn, C. G., Umney, N. D., & Yazdanbakhsh, M. (1982). Effects of ethanol administration on platelet function in the rat. *Alcoholism: Clinical and Experimental Research, 6*, 512–519. https://doi.org/10.1111/j.1530-0277.1982.tb05015.x.

Liu, L., Chen, M., Zhao, L., Zhao, Q., Hu, R., Zhu, J., et al. (2017). Ethanol induces platelet apoptosis. *Alcoholism: Clinical and Experimental Research, 41*, 291–298. https://doi.org/10.1111/acer.13295.

Llinás, S. G., Caballero, A. J., Penalver, J. C., & Valdes, R. (2014). Platelet serotonin concentration and clinical status in alcohol withdrawal syndrome, preliminary results. *MEDICC Review, 16*, 37–42.

Lustenberger, T., Inaba, K., Barmparas, G., Talving, P., Plurad, D., Lam, L., et al. (2011). Ethanol intoxication is associated with a lower incidence of admission coagulopathy in severe traumatic brain injury patients. *Journal of Neurotrauma, 28*, 1699–1706. https://doi.org/10.1089/neu.2011.1866.

Malik, F., & Wickramasinghe, S. N. (1986). Haematological abnormalities in mice continuously exposed to ethanol vapour. *British Journal of Experimental Pathology, 67*, 831–838.

Manappallil, R. G. (2016). Acute onset pancytopenia following alcohol heavy drinking. *Asian Journal of Bio-Medical Research, 2*, 6–7 [S.l.], v. 2, apr. 2016. ISSN 2454-6275. Available at: https://www.researchgate.net/publication/303805070_Acute_onset_pancytopenia_following_alcohol_heavy_drinking.

Mandyam, C. D., Villalpando, E. G., Steiner, N. L., Quach, L. W., Fannon, M. J., & Somkuwar, S. S. (2017). Platelet endothelial cell adhesion molecule-1 and oligodendrogenesis: Significance in alcohol use disorders. *Brain Sciences, 7*. https://doi.org/10.3390/brainsci7100131.

Mayo-Smith, M. F., & Bernard, D. (1995). Late-onset seizures in alcohol withdrawal. *Alcoholism: Clinical and Experimental Research, 19*, 656–659. https://doi.org/10.1111/j.1530-0277.1995.tb01563.x.

Mikhailidis, D. P., Jenkins, W. J., Barradas, M. A., Jeremy, J. Y., & Dandona, P. (1986). Platelet function defects in chronic alcoholism. *British Medical Journal, 293*, 715–718. https://doi.org/10.1136/bmj.293.6549.715.

Mitchell, O., Feldman, D. M., Diakow, M., & Sigal, S. H. (2016). The pathophysiology of thrombocytopenia in chronic liver disease. *Hepatic Medicine: Evidence and Research, 8*, 39–50. https://doi.org/10.2147/hmer.S74612.

Monte, R., Rabunal, R., Casariego, E., Bal, M., & Pertega, S. (2009). Risk factors for delirium tremens in patients with alcohol withdrawal syndrome in a hospital setting. *European Journal of Internal Medicine, 20*, 690–694. https://doi.org/10.1016/j.ejim.2009.07.008.

Nair, M., Maria, J. M., Agudelo, M., Yndart, A., & Vargas-Rivera, M. E. (2015). Platelets contribute to BBB disruption induced by HIV and alcohol. *Journal of Alcoholism and Drug Dependence, 3*, 182. https://doi.org/10.4172/2329-6488.1000182.

Nakao, S., Harada, M., Kondo, K., Mizushima, N., & Matsuda, T. (1991). Reversible bone marrow hypoplasia induced by alcohol. *American Journal of Hematology, 37*, 120–123. https://doi.org/10.1002/ajh.2830370210.

Niemirowicz, K., Żelazowska-Rutkowska, B., Wysocka, J., & Car, H. (2012). Zaburzenia liczby płytek krwi. *Journal of Laboratory Diagnostics, 48*, 455–460.

Numminen, H., Hillbom, M., & Juvela, S. (1996). Platelets, alcohol consumption, and onset of brain infarction. *Journal of Neurology, Neurosurgery, and Psychiatry, 61*, 376–380. https://doi.org/10.1136/jnnp.61.4.376.

Paniccia, R., Priora, R., Liotta, A. A., & Abbate, R. (2015). Platelet function tests: A comparative review. *Vascular Health and Risk Management, 11*, 133–148. https://doi.org/10.2147/vhrm.S44469.

Paraf, A., Coste, T., & Gouffier, E. (1971). [Disorders of hematopoiesis in acute alcoholism]. *Presse Medicale, 79*(49), 2219–2220.

Peck-Radosavljevic, M. (2017). Thrombocytopenia in chronic liver disease. *Liver International, 37*, 778–793. https://doi.org/10.1111/liv.13317.

Peltz, S. (1991). Severe thrombocytopenia secondary to alcohol use. *Postgraduate Medicine, 89*, 75–76. https://doi.org/10.1080/00325481.1991.11700918, 85.

Post, R. M., & Desforges, J. F. (1968a). Thrombocytopenia and alcoholism. *Annals of Internal Medicine, 68*, 1230–1236. https://doi.org/10.7326/0003-4819-68-6-1230.

Post, R. M., & Desforges, J. F. (1968b). Thrombocytopenic effect of ethanol infusion. *Blood, 31*, 344–347.

Psaltopoulou, T., Sergentanis, T. N., Ntanasis-Stathopoulos, I., Tzanninis, I. G., Tsilimigras, D. I., & Dimopoulos, M. A. (2018). Alcohol consumption and risk of hematological malignancies: A meta-analysis of prospective studies. *International Journal of Cancer, 143*, 486–495. https://doi.org/10.1002/ijc.31330.

Rauchenzauner, M., Kountchev, J., Ulmer, H., Pechlaner, C., Bellmann, R., Wiedermann, C. J., et al. (2005). Disturbances of electrolytes and blood chemistry in acute alcohol intoxication. *Wiener Klinische Wochenschrift, 117*, 83–91. https://doi.org/10.1007/s00508-004-0280-0.

Rozenberg, G. (2011). *Cases in Microscopic Haematology*. Elsevier Publishing.

Rubin, R., & Rand, M. L. (1994). Alcohol and platelet function. *Alcoholism: Clinical and Experimental Research, 18*, 105–110. https://doi.org/10.1111/j.1530-0277.1994.tb00888.x.

Ruf, J. C. (2004). Alcohol, wine and platelet function. *Biological Research, 37*, 209–215. https://doi.org/10.4067/s0716-97602004000200006.
Ryback, R., & Desforges, J. (1970). Alcoholic thrombocytopenia in three inpatient drinking alcoholics. *Archives of Internal Medicine, 125*, 475–477.
Sahud, M. A. (1972). Platelet size and number in alcoholic thrombocytopenia. *New England Journal of Medicine, 286*, 355–356. https://doi.org/10.1056/nejm197202172860706.
Saitz, R., Mayo-Smith, M. F., Roberts, M. S., Redmond, H. A., Bernard, D. R., & Calkins, D. R. (1994). Individualized treatment for alcohol withdrawal. A randomized double-blind controlled trial. *Journal of the American Medical Association, 272*, 519–523.
Scharf, R. E., & Aul, C. (1988). [Alcohol-induced disorders of the hematopoietic system]. *Zeitschrift fur Gastroenterologie, 26*(Suppl 3), 75–83.
Schmidt, P. M. (1983). [Hematologic anomalies in alcoholic cirrhosis]. *Schweizerische Medizinische Wochenschrift, 113*, 1025–1030.
Schneider, I., & Krautzig, S. (2009). *Choroby wewnętrzne. Seria na Dyżurze. Normy I normogramy*. Elsavier: Urban & Partner, ISBN 978-83-7609-184-6.
Sekhon, S. S., & Roy, V. (2006). Thrombocytopenia in adults: A practical approach to evaluation and management. *Southern Medical Journal, 99*, 491–498. https://doi.org/10.1097/01.smj.0000209275.75045.d4. quiz 499–500, 533.
Sharathkumar, A., & Shapiro, A. (2008). Platelet function disorders. *Treatment of Hemophilia, 9*, 1–22.
Sheikh, M. Y., Raoufi, R., Atla, P. R., Riaz, M., Oberer, C., & Moffett, M. J. (2012). Prevalence of cirrhosis in patients with thrombocytopenia who receive bone marrow biopsy. *Saudi Journal of Gastroenterology, 18*, 257–262. https://doi.org/10.4103/1319-3767.98431.
Shen, G., Gao, Y., Lee, K. Y., & Nan, G. (2018). Primary medullary hemorrhage in a patient with coagulopathy due to alcoholic cirrhosis: A case report. *Medicine (Baltimore), 97*, e0292. https://doi.org/10.1097/md.0000000000010292.
Silczuk, A., Habrat, B., & Lew-Starowicz, M. (2019). Thrombocytopenia in patients hospitalized for alcohol withdrawal syndrome and its associations to clinical complications. *Alcohol and Alcoholism, 54*, 503–509. https://doi.org/10.1093/alcalc/agz061.
Smith, C. M., 2nd, Tobin, J. D., Jr., Burris, S. M., & White, J. G. (1992). Alcohol consumption in the Guinea pig is associated with reduced megakaryocyte deformability and platelet size. *The Journal of Laboratory and Clinical Medicine, 120*, 699–706.
Smith, C., Gasparetto, M., Jordan, C., Pollyea, D. A., & Vasiliou, V. (2015). The effects of alcohol and aldehyde dehydrogenases on disorders of hematopoiesis. *Advances in Experimental Medicine & Biology, 815*, 349–359. https://doi.org/10.1007/978-3-319-09614-8_20.
Soegaard, N., & Ingeberg, S. (1985). [Alcoholic thrombocytopenia]. *Ugeskrift for Lager, 147*, 2833.
Stephan, F., Montblanc, J., Cheffi, A., & Bonnet, F. (1999). Thrombocytopenia in critically ill surgical patients: A case-control study evaluating attributable mortality and transfusion requirements. *Critical Care, 3*, 151–158. https://doi.org/10.1186/cc369.
Stobbe, H. (1981). [Alcohol and hematopoiesis]. *Zeitschrift fur die Gesamte Innere Medizin und ihre Grenzgebiete, 36*, 571–577.
Strate, L. L., Singh, P., Boylan, M. R., Piawah, S., Cao, Y., & Chan, A. T. (2016). A prospective study of alcohol consumption and smoking and the risk of major gastrointestinal bleeding in men. *PloS One, 11*, e0165278. https://doi.org/10.1371/journal.pone.0165278.
Straub, P. W. (1985). [Alcohol and the blood]. *Schweizerische Medizinische Wochenschrift, 115*, 1753–1759.
Stuart, M. J. (1979). Ethanol-inhibited platelet prostaglandin synthesis in vitro. *Journal of Studies on Alcohol, 40*, 1–6. https://doi.org/10.15288/jsa.1979.40.1.
Sullivan, L. W., & Herbert, V. (1964). Suppression hematopoiesis by ethanol. *Journal of Clinical Investigation, 43*, 2048–2062. https://doi.org/10.1172/jci105079.
Sullivan, L. W., Liu, Y. K., & Talarico, L. (1968). Alcohol induced thrombocytopenia in man. *Journal of Clinical Investigation, 47*, 95a.
Takahashi, S., Tani, N., & Yamane, H. (1976). Monoamine oxidase activity in blood platelets in alcoholism. *Folia Psychiatrica et Neurologica Japonica, 30*, 455–462. https://doi.org/10.1111/j.1440-1819.1976.tb02668.x.
Visentin, G. P., & Liu, C. Y. (2007). Drug-induced thrombocytopenia. *Hematology-Oncology Clinics of North America, 21*, 685–696. https://doi.org/10.1016/j.hoc.2007.06.005. vi.
Vo, Q. T., & Thompson, D. F. (2019). A review and assessment of drug-induced thrombocytosis. *The Annals of Pharmacotherapy, 53*, 523–536. https://doi.org/10.1177/1060028018819450.
Wang, L., Wu, Q., Fan, Z., Xie, R., Wang, Z., & Lu, Y. (2017). Platelet mitochondrial dysfunction and the correlation with human diseases. *Biochemical Society Transactions, 45*, 1213–1223. https://doi.org/10.1042/bst20170291.
Wasiluk, A., & Jasińska, E. (2010). Parametry morfologiczne i czynnościowe płytek krwi noworodków i osób dorosłych. *Journal of Laboratory Diagnostics, 46*, 325–329.
Wilson, J. H. (1980). Alcoholic thrombocytopenia: A brief review. *Journal - Oklahoma State Medical Association, 73*, 13–17.
Yokoyama, A., Yokoyama, T., Mizukami, T., Matsui, T., Kimura, M., Matsushita, S., et al. (2017). Platelet counts and genetic polymorphisms of alcohol dehydrogenase-1B and aldehyde dehydrogenase-2 in Japanese alcoholic men. *Alcoholism: Clinical and Experimental Research, 41*, 171–178. https://doi.org/10.1111/acer.13283.
Zamir, D., Polychuck, I., Leibovitz, I., Reitblat, T., Ducach, A., & Lugassy, G. (2004). Thrombotic thrombocytopenic purpura due to alcohol binge drinking. *European Journal of Internal Medicine, 15*, 262–263. https://doi.org/10.1016/j.ejim.2004.04.008.
Zhang, Q. H., Das, K., Siddiqui, S., & Myers, A. K. (2000). Effects of acute, moderate ethanol consumption on human platelet aggregation in platelet-rich plasma and whole blood. *Alcoholism: Clinical and Experimental Research, 24*, 528–534.