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The effects of alcohol on gastrointestinal tract, liver and pancreas: evidence-based suggestions for clinical management

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Abstract. – Alcohol has a direct impact on the digestive system due to its contact with mucosal lining and interference with digestive functions. Various diseases of the gastrointestinal tract, including tumors, may be related to an excess of alcohol intake and the relationship between alcohol abuse and hepatic and pancreatic damage is well established. According to WHO, alcohol and alcohol-related diseases represent a major health problem and will probably continue to do so in the foreseeable future.

In this review, we summarize the present knowledge on clinically relevant alcohol-related problems in order to provide practicing physicians with evidence-based general suggestions which might help in the management of alcohol-related gastrointestinal disorders.

A thorough clinical history together with a number of questionnaires are essential for detecting alcohol dependence or abuse. Biochemical tests (nonspecific and specific) have been considered to be less sensitive than questionnaires in screening for alcohol abuse, but they may be useful in identifying relapses. Protracted behavior modification, cognitive behavioral therapy, psychological counseling, and mutual support groups have been considered the most effective long-term treatments. Several drugs have been developed that are able to interfere with the neurotransmitters involved in craving mechanisms, and we summarize the evidence of their efficacy to increase abstinence and to prevent relapse.

Key Words:
Alcohol dependence, Alcohol abuse, Cancer, Alcoholic gastrointestinal diseases, Alcoholic liver diseases.

Introduction

Alcohol consumption is one of the main risk factors for health, one of the major causes of liver cirrhosis, and the third leading cause of premature death in Europe. Additionally, it is listed as a cause of approximately 60 illnesses and pathological conditions, including cancer. In every country, the overall cost of alcohol-related problems every year accounts for more than 1% of the gross domestic product. Each year, at least 2.3 million people die with an alcohol-related problem[1]. In Europe, 55 million people are alcohol consumers, and 23 are million alcohol-dependent. Alcohol-related mortality represents approximately 6.3% of all deaths registered in 2002 – twice the world average[2].

Each year, 25% of deaths among males aged 15-29 years and 10% of deaths among young women are caused by wrongful alcohol consumption, and 4%-6% of disabilities worldwide are attributable to alcohol. Since 2000, there has been an increase in alcohol consumption among young people and in women. From 2001 to 2002, there was an increase of 2.8 in the rates of total alcohol-

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attributable hospitalization and hospital discharges for diseases fully attributable to alcohol in the age range 0-14 years, across all Italian regions[3].

In January 2010, the World Health Organization (WHO) issued a document intended to reduce the risks of alcohol consumption, labelling alcohol an "avoidable" risk factor[4]. The goals of the document were numerous, including community-based programs, policies related to driving, and a reduced availability of alcohol, at their price.

The consumption of alcoholic beverages has a direct impact on the digestive system due to its contact with the mucous membranes, the absorption and metabolism of ethanol and its interference with digestive function and the intestinal flora.

We have summarized the present knowledge of clinically relevant alcohol-related problems in the hopes of assisting our peers in the diagnosis and management of alcoholic gastrointestinal and liver diseases. This paper, intended for use by practicing physicians, offers evidence-based general suggestions, which may be modulated in individual cases.

Methodology

This document represents the synthesis of a review of the literature. To this end, the pertinent literature was first reviewed, paying particular attention to evidence-based classifications. Based on the national plan for guidelines[5], the levels of evidence range from I to VI, and the strength of a recommendation ranges from A to E (Table I). If no clear evidence exists, guidance was based on the consensus among the members of the Committee.

Epidemiology of Alcohol Consumption in Italy

Until a few years ago, two types of drinking culture existed in Europe: that of Northern Europe (the culture of "dry") and that of Southern Europe (the culture of "wet"). These cultures diversified the occasions and the methods of drinking, the types of beverages consumed, the meanings attributed to alcohol, and the intensity and orientation of political control. Italy, until a few years ago, was considered an exponent of "wet culture", in which the mode of consumption was traditionally linked to the meal, and drinking was integrated into everyday life[6]. Despite the decrease in the average per capita consumption observed in Italy in the past twenty years, certain national indicators have allowed the identification of a large segment of the population with consumption risks exceeding the recommended limits of 1-2 units of alcohol for women and 2-3 for males (see later)[6]. Upon consideration of the age classes (ages 14 and up), we were able to identify the highest prevalence and number of nonmoderate consumers in the age groups 45-64 and 65-74, for both sexes. Actually, in Italy, as in other European countries, the consumption of alcoholic beverages is increasing among young people and women; the threshold of onset (i.e., 11-12 years) appears to be the lowest in Europe. The intake of alcohol, unlike in the past, is no longer concentrated only in the weekends, but instead is spreading to other days of the week each year, implicating approximately 800,000 people under the legal age of 16 years. In Italy, one's first alcohol con-

Table I. Levels of evidence and strength of recommendations.

Levels of evidence	
I	Evidence from multiple RCTs and or systematic reviews of randomized studies
II	Evidence from a single well-designed controlled trial
III	Evidence from non-randomized cohort studies with concurrent or historical controls or their metanalytic review
IV	Evidence from retrospective studies or their metanalytic review
V	Evidence from case series without a control group
VI	Evidence from Expert opinion or Expert Committees as indicated in guidelines or Consensus Conferences or based on the opinions of individual members of Expert Committees responsible for writing guidelines
Strength of recommendations	
A	Procedure/diagnostic test strongly recommended, supported by good quality scientific evidence, even if not necessarily type I or II
B	Procedure/diagnostic test not invariably recommended but to be carefully considered
C	Procedure/diagnostic test surrounded by substantial uncertainty
D	Procedure not recommended
E	Procedure strongly advised against

sumption usually occurs during preadolescence[7], often within the family context during meals associated with celebrations. In spite of the traditional drinking habits in Italy, some recent studies have stressed that the style of alcohol consumption among Italian adolescents is rapidly changing[8,9]. While wine is preferred during meals, on weekdays and in the family context, the consumption of beer and spirits during weekends with friends and outside of mealtime is gradually increasing[10].

The periods of "binge drinking" (a consumption of at least 5 alcoholic drinks between meals and in a period of approximately 2 hours) are concentrated on Saturdays (50% of males and 41% of females), and the most represented age group is between 16 and 19 years. Additionally, girls are binge-drinkers less often than males (6.1% vs 14.6%, respectively)[11,12]. The problem of binge-drinking is becoming widespread among Italian young adults; recently, the Italian Government, to fight the growing problem of binge-drinking and alcohol-related deaths, has adopted many measures, including zero tolerance for drivers and strict controls at discos.

Level of evidence: I

Alcohol Consumption and the Daily Clinical Practice

Alcohol and alcohol-related diseases, in the present and for the foreseeable future, represent an increasingly major problem, both for general medical practice and for other specialties. However, their true impact is often underestimated, and their management is particularly difficult due to a lack of resources and synergies within the structures of the Health Service in our country. In particular, we believe it will be very useful to look into what is, at present, the primary approach to the problem by general practitioners.

The data derived from analysis of the item "alcohol" in computerized registration folders for general practitioners, as reported in the Health Search database and generated by 908 researchers (data not published), report the following:

– the contribution of alcohol consumption is often underestimated in the anamnesis of the patient;
– alcohol consumption is higher in males and increases with age, mostly in age classes above 35 years;
– the percentage of alcohol consumption was found to be higher in subjects with gout and fatty livers.

In a recent work, Loguercio et al[13] examined the registration of the item alcohol by 104 physicians among approximately 150000 patients. In this project, 94/104 physicians participated in the study by performing an alcohol history of their patients. Among the data collected, however, regular use of alcohol was found in 19.6% of the patients examined; in 11.7% of these, alcohol consumption exceeded 200 g of pure ethanol per week, and 6550 patients were suffering from various types of chronic liver disease (34% steatosis). The item "alcohol" among all patients affected by liver disease was evaluated in 1334 cases (20%); the average consumption was 114 g/week (approximately 16 g/day), range 0-6652. In patients with fatty liver disease, "alcoholic" steatosis was the 1.1%. This study shows that the data recording by general practitioners in chronic liver disease patients lacks homogeneity and can miss important information. One unmet need is therefore the integration between theoretical knowledge and practice to share similar behaviors and to improve the management of these patients.

Level of evidence: IV

Alcohol and Digestive System

Esophagus

Different epidemiological studies have demonstrated a strong association between chronic alcohol consumption and the development of esophageal diseases, such as esophagitis, Barrett's esophagus[14-19] and precancerous lesions (columnar metaplasia and dysplasia)[20,21]. In fact, regular alcohol consumption has been recognized as a risk factor for the development of gastroesophageal reflux disease (GERD) and its related complications[16-21] because ethanol seems to promote alterations of the propulsive motility of distal esophagus and the dysfunction of lower esophageal sphincter (LES).

Other studies have reported conflicting results[22-25], in particular regarding the moderate consumption of red wine, which seems to protect from epithelial metaplasia or dysplasia[24] due to its high content of polyphenols, in particular resveratrol, which exerts an antioxidant action[25].

Alcohol represents one of the most important risk factors for esophageal neoplasia[26], in particular in Western countries[27]. It represents a strong risk factor for squamous-cell carcinoma, with a clear dose-response relationship. The relative risk for heavy drinkers (≥ 75 g/day of pure ethanol) is 7.65 (95% CI, 3.16-18.49) times that of never-

drinkers, although moderate consumption of wine or beer (1-24 g/day or a beer) is not associated with a significantly increased risk.

Epidemiological evidence of a putative association between alcohol consumption and the development of esophageal adenocarcinoma are not univocal, as the absence of a significant[17,23,28-30] or a protective role of red wine[17,23] and an increased risk only for habitual consumers of distilled liquors[29] have also been reported. Recent evidence suggests the need for further studies to confirm, or exclude, ethanol as a risk factor for the development of esophageal adenocarcinoma[18].

In brief, alcohol is a risk factor for:
– erosive esophagitis (level of evidence: III-IV)
– adenocarcinoma (conflicting results) (level of evidence: III)

Stomach

A possible association between chronic alcohol consumption and the risk of chronic gastritis has been proposed[19,31], but this link has not been well demonstrated in particular when alcohol consumption is considered separately from other potential risk factors for gastritis[19,32].

On the other hand, it seems that there is an inverse correlation between alcohol consumption and the prevalence of *H. pylori* infection[33-35].

In fact, a moderate alcohol consumption appears to act as a protective factor against *H. pylori* infection, most likely because alcoholic beverages have many direct and indirect effects on the gastric mucosa, gastric emptying, and gastric acid secretion that may affect the living conditions of the bacterium[33]. At the same time, these factors could promote its elimination[35].

Moreover, a moderate alcohol consumption could positively influence the efficacy of eradication therapy[36,37].

The association between alcohol consumption and the risk of peptic disease is still controversial[38,39,40]; a positive correlation between a large amount of ethanol and peptic ulcer disease has been found[39,40], even if the link did not reach significance when alcohol drinking is considered separately from other risk factors for peptic disease[19,38,39].

Different prospective and retrospective studies failed to demonstrate a significant increase in the risk for gastric cancer in subjects who habitually consume alcoholic beverages[21,41]; neither the cumulative amount nor the type of alcoholic beverages seemed to exert a positive influence on this association.

A recent meta-analysis, on the contrary, found a slightly increased relative risk (1.20) for heavy drinkers (≥4 drinks per day), mainly for gastric non-cardia adenocarcinoma[42].

Ethanol exerts some direct and indirect effects on the gastric physiology. Alcohol intake reduces gastric motility in a not strictly dose-dependent manner[43], but motility is mostly influenced by the non-alcoholic compounds of alcoholic beverages. Drinks produced by fermentation prolong half gastric emptying times more than an equivalent ethanol solution, while for distilled alcoholic beverages, the difference is not significant[43].

Only alcoholic beverages produced by fermentation seem to enhance gastric acid secretion[44,45], and this effect is most likely due to non-alcoholic compounds, such as succinic and maleic acids[46].

In brief, alcohol is a risk factor for:
– chronic gastritis (level of evidence: III)
– gastric or duodenal peptic ulcer (conflicting results) (level of evidence: III)
– gastric cancer (conflicting results) (level of evidence: III)

Small Bowel

Most of the ingested ethanol is absorbed by passive diffusion through the duodenal and jejunal mucosa; consequently, proceeding from the duodenum to ileum, both the intraluminal ethanol concentration and the trans-mucosal gradient progressively decrease[47]. These observations suggest that the interaction between ingested ethanol and intestinal mucosa is more pronounced in the upper tract of the small bowel, where the intraluminal concentration is higher and the absorbed portion is more significant[47]. Acute ethanol ingestion is associated with the apical erosion of intestinal villi, separation of the epithelium from the basal layer with formation and subsequent rupture of sub-epithelial blisters and the discontinuation of epithelial barrier[48]. These effects are transient, because epithelial regeneration allows a complete reparation of damages within 24-48 hours[48].

The increased intestinal permeability in alcoholics is associated with two important consequences: an increased translocation of macromolecules from the lumen to the blood[49] and a reduced capacity for mucosal absorption, associated with a more pronounced intestinal luminal secretion[47]. An increased translocation of endotoxins, such as lipopolysaccharides (LPS), to blood circulation is also promoted by the increased

prevalence of small bowel bacterial overgrowths in alcoholics due to both an altered motility and a decreased immuno-mediated bacterial clearance from the gut[47,50,51].

Alcohol consumption interferes with the absorption of macronutrients, such as glucose, amino acids and lipids[48], and of micronutrients, such as folic acid, which is crucial for the proper maturation and function of epithelial intestinal cells, thus creating a vicious circle[48]. These effects are transient. In fact, abstention from alcoholic beverages is associated with the complete restoration of gut epithelial morphology and functionality[48].

The acute ingestion of alcoholic beverages promotes a reduction of segmental contractile activity and an increase of propulsive motility, through both direct and indirect effects on local musculature[48] and nervous plexus[52]; these effects promote a reduction of the intestinal transit time, a decrease of absorptive functions and, eventually, the appearance of diarrhea[48]. Additionally, a small intestinal bacterial overgrowth contributes to the onset of diarrhea.

In clinical settings, there is a significant correlation between the effects of alcohol on the gut mucosa and symptoms. In alcoholics, the appearance of steatorrhea is related to lipid malabsorption, alcohol-related pancreatic dysfunction, small intestinal bacterial overgrowth, cholestasis and alteration of the bile acid metabolism[53]. Alcoholic osteopathy is related to vitamin D malabsorption[53]. Furthermore, possible protein malnutrition is linked to amino acid malabsorption and increased catabolism[47,48,53,54]; Wernicke-Korsakoff encephalopathy is related to thiamine deficiency; peripheral neuropathy and funicular myelosis are secondary to a vitamin B12 deficiency, and muscle cramps are due to magnesium deficiency[53].

In brief, alcohol has the following effects:
- *increases intestinal permeability (level of evidence: III)*
- *increases propulsive motility (level of evidence: III)*
- *reduces capacity of mucosal absorption (level of evidence: III)*

Colon and Rectum

Prospective studies have demonstrated a significant association between alcohol consumption and the risk for colorectal cancer[55-60]. This risk seems to become significantly higher when the cumulative alcohol consumption exceeds the threshold value of 30 g/day[55,59], but recent evidence suggests that a significant risk for carcinogenesis is present even for lower levels of alcohol consumption per day (from 3.6 g/day to 14 g/day).

A recent cohort study[59] confirmed the increased risk for colorectal cancer in heavy drinkers (>30 g/day) but suggested that the most influential factor was represented by the length of the period of heavy consumption, as the subjects at major risk were heavy-drinkers with a history of abuse for at least 5 years. Moreover, the occurrence of cancer in these subjects was more elevated in the rectum (HR = 1.12, 95% CI = 1.06-1.18) than in the distal or proximal colon; sex and the type of alcoholic beverages did not exert any influence[59].

Regarding the risk for colorectal adenoma**,** alcohol consumers do not have a significantly higher risk for colorectal adenoma than non-drinkers. However, a long duration of alcohol consumption is associated with a higher risk for advanced adenoma (OR = 2.0, 95% CI: 1.10, 3.64 for >28 years of consumption *vs* no drinkers) and the development of 3 or more adenomas, often located in multiple anatomic sites[60].

In brief, alcohol has the following effect:
- *increases the risk for colorectal cancer, especially in subjects with a long-lasting alcohol abuse (level of evidence: III)*

Pancreas

Alcohol still represents the second most common cause of acute pancreatitis, after gallstones[61]. The risk for pancreatitis increases in proportion with the volume of alcohol consumption, reaching an exponential correlation after the threshold of 5 drinks/day. For heavy drinkers (5 or more drinks/day), the hazard ratio is approximately 3.0 *vs* abstainers[62].

The frequency of sex and drinking do not influence the risk for acute pancreatitis[62,63]. Regarding the type of alcoholic beverages, there is a dose-response association between the amount of spirits consumed on a single occasion and the risk of acute pancreatitis. In fact, this risk is increased by approximately 52 per cent (risk ratio 1.52, 95% CI 1.12 to 2.06) for every increment of five standard drinks of spirits consumed on a single occasion. No association is found between wine and beer consumption and acute pancreatic injury[63].

Some evidence has demonstrated that alcoholic pancreatitis does not completely resolve[64-69]; in fact, the risk of acute pancreatitis recurrence is significantly higher in male patients who

are younger than 40 yr and had an alcoholic etiology of their pancreatitis. Such patients have an annual relapse rate of 5.3%[65]. Other prospective studies confirmed these results, reporting a significantly higher risk of recurrence, progression to chronic pancreatitis and development of diabetes mellitus in alcoholic pancreatitis, when compared with pancreatitis of different etiologies[66]. Furthermore, the risk of recurrence was associated with age < 45 yr, mild severity of the first attack, the period of the first 4 years after the first episode and, in particular, a tendency for higher and continued alcohol consumption[67].

The cumulative risk of progression from alcohol-related acute to chronic pancreatitis is approximately 15% at 10 years, and this risk progressively increases after each recurrent attack[65].

Many processes are potentially involved in alcohol-related pancreatic injury. Ethanol induces the secretion of a more viscous juice and promotes the formation of protein plugs[68], "sensitizes" acinar cells' inflammatory response through the activation of the pro-inflammatory cascade[64], and promotes acinar cell death by necrosis, instead of apoptosis, through mitochondrial and lysosomal dysfunction[64]. Its metabolites [fatty acid ethil esters (FAEEs)] contribute to increased acinar cell injury[64].

Ethanol seems to contribute not only to initiation of pancreatic injury but also to its perpetuation through the dysregulation of the immuno-inflammatory response, in particular in the presence of genetic and environmental co-factors. These could explain the ethanol-induced impairment of pancreatic recovery/regeneration from the first episode of acute pancreatitis, which promotes the transition to chronic pancreatic injury and fibrosis through the recruitment of pancreatic stellate cells[64].

Alcohol consumption, in fact, still represents the first cause of chronic pancreatitis[70]; However, recent studies have found that alcohol abuse represents a major risk factor for chronic pancreatitis in only 34%[71], or 44%[72] cases.

The risk of chronic pancreatitis increases with the amount and duration of drinking. A minimum of 6 to 12 years of approximately 80 g or more of ethanol per day is considered necessary for the development of clinically significant disease[72]. However, less than 10% of alcohol abusers develop chronic pancreatitis[70], suggesting that other individual factors influence alcohol toxicity and the susceptibility to developing chronic diseases, such as tobacco smoking, body mass index and genetic polymorphism.

Different studies have tried to find a correlation between pancreatic cancer risk and alcohol consumption, reporting no[73] or a weak[74] association. Other prospective studies identified an increased risk of cancer in heavy alcohol consumers, for example, a 22% increased risk in subjects consuming ≥30-40 g ethanol per day[75] and an OR = 1.6, 95% confidence interval 1.2-2.2 for subjects drinking ≥9 drinks per day[76]. This association remained significant, even considering alcohol consumption separate from tobacco smoking[76]. Furthermore, alcohol consumption, specifically liquor consumption of 3 or more drinks per day, increases pancreatic cancer mortality independently of smoking. Thus, considering the weak association between alcohol consumption and pancreatic cancer and the strong relationship between alcohol abuse and smoking habits, the latter could represent a confounding factor. Consequently, alcohol would be responsible for only a small fraction of pancreatic cancers.

In brief, alcohol has the following effects:

– *increases the risk for acute and chronic pancreatitis and for pancreatic cancer and this parallels the entity of alcohol consumption (level of evidence: III)*

Liver

Alcoholic liver disease (ALD) comprises a large spectrum of alcohol-related liver diseases, ranging from fatty liver or simple steatosis to alcoholic hepatitis, chronic hepatitis with hepatic fibrosis or cirrhosis[77].

Fatty liver develops in approximately 90% of individuals who drink more than 60 g/day of alcohol, but this condition is completely reversible after 4-6 weeks of abstinence, even if fibrosis and cirrhosis develop in 5-10% of patients, despite abstinence[77,78].

A persistent alcohol intake >40 g/day increases the risk of developing fibrosis and cirrhosis by 30-40%[77,78]. Perivenular fibrosis, which represents a significant and independent risk factor for the progression to fibrosis and cirrhosis, occurs in patients who ingest more than 40 g/day for an average of 25 years[77].

Alcoholic hepatitis represents a spectrum of diseases, ranging from mild injury to severe and life-threatening damage, which occur only in a subset of alcoholics (approximately 10% to 35%). These typically occur in individuals with a long-standing history of consuming more than 100 g/day of alcohol for at least two decades[79].

This condition may occur even when alcohol consumption has been significantly reduced or stopped[80]. Although alcoholic hepatitis can occur in a mild form, patients are at high risk for developing progressive liver injury, as cirrhosis develops in up to 50%[77]. Abstinence from alcohol is associated with histological normalization in 27% of patients, with progression to cirrhosis in 18% and with persistent alcoholic hepatitis in the remainder[77].

As far as the type of beverages is concerned, beer and spirits seem to be more dangerous than wine[81], while drinking outside the meal and binge-drinking (defined as five drinks for men or four drinks for women in one sitting) increase the risk for ALD[77]. Women seem to be twice as sensitive to alcohol-mediated hepatotoxicity and may develop more severe ALD at lower doses and with shorter durations of alcohol consumption than men[82]. This can be a consequence of their relative lower amount of gastric alcohol dehydrogenase, their higher proportion of body fat or the changes in alcohol absorption during the menstrual cycle[77]. However, men are twice as likely to abuse alcohol compared to women, and so ALD is more frequent in men[79].

Obesity, protein and micronutrient deficiency and coexisting HCV infections represent factors that strengthen the damaging effects of alcohol on the liver[77,79].

The genetic polymorphisms of alcohol dehydrogenase and their interactions with the genes involved in generating and detoxifying free radicals also influence the susceptibility to alcoholic liver disease[77].

The first step of alcohol-induced liver damage is the development of hepatic steatosis as a result of the impairment of fat synthesis, accumulation, mobilization and breakdown[77]. The second step is the induction of inflammation, cell injury and apoptosis, all of which contribute to steatohepatitis. Stored free fatty acids promote oxidative stress and hepatocyte apoptosis; ethanol induces cytochrome P4502E1, producing toxic acetaldehyde and reactive oxygen species; gut-derived endotoxins (the translocation of which is promoted by alcohol-induced gut dysbiosis and mucosal barrier function impairment) activate Kupffer cells, producing pro-inflammatory cytokines[80]. The last step is the deposition of the fibrosis by hepatic stellate cell activation.

In industrialized countries, high alcohol consumption represents one of the most important risk factors for developing liver cirrhosis and hepatocellular carcinoma (HCC). In general, alcohol consumption is associated with a 2-fold increase in the individual risk of HCC development[83], reaching an increase of 5 or 7-fold in cases of an intake >80 g/day for up to 10 years[84]. The cumulative risk appeared to be doubled in the presence of HCV infection, thus underlying the synergistic effects of these two risk factors[85]. Chronic alcohol consumption promotes hepatic carcinogenesis, not only inducing chronic inflammation, hepatocyte necrosis and regeneration, but also leading to the exertion of the procarcinogenic effects of the main metabolite, acetaldehyde, due to its direct interaction with the hepatocytes' DNA[84].

In brief, alcohol has the following effects:
- *increases the risk of liver fibrosis and cirrhosis (level of evidence: III)*
- *increases the risk of HCC (level of evidence: III-IV)*

Alcohol and nutrition

Alcohol is a macronutrient with a high energy content; however, its utilization as an energy source is a low-efficient process. Due to its low nutritional value and metabolization through so-called "futile cycles", calories derived from alcohol are considered "empty calories". Furthermore, the energy use of ethanol may be ineffective due to the activation of the microsomal oxidation system and to increases in alcohol-induced thermogenesis[86].

The most frequent presentation of alcoholic patients is under-nutrition, to varying degrees[87,88] although an increased alcohol consumption may sometimes be associated with the presence of overweight and obesity. In a large epidemiological survey on alcohol intake, nutritional status and dietary habits, in the US population, high levels of alcohol consumption were associated with decreased body weight and body mass index and a lower percentage of body fat in men[89].

The origin of malnutrition is multifactorial. The factors involved are the replacement of calories from food with those from alcohol (primary malnutrition), as well as an alteration in nutrients' metabolism and absorption because of the toxic effect of alcohol on the liver and the gastrointestinal tract (secondary malnutrition). Alcohol, in its anorectic effects, leads to a loss of interest in food; in fact, some of the factors that regulate appetite, such as ghrelin and leptin, may be altered in alcoholics, adversely affecting the desire to eat[90,91].

The analysis of the dietary interviews in a large series of alcoholic patients revealed that, with increasing alcohol consumption, the macronutrient intakes decrease; carbohydrate intake is the first to be affected[92].

Dietary intake in alcoholic patients is also influenced by socio-economic factors, and malnutrition is more frequent in alcoholic males of low socio-economic classes. At the same time, heavy drinking frequently induces social or familial derangement, leading to alterations in life styles and irregular feeding habits. Irregular feeding habits and decompensated liver cirrhosis were the only variables that independently predicted malnutrition in a large series of male alcoholic patients[93]. Subjects who started abusing alcohol before 15 years of age may present a shorter height due to the alteration of their normal process of growth[93].

Several alterations in the metabolisms of carbohydrates, fats and proteins have been described in relation to alcohol abuse, particularly when liver damage arises. Concerning carbohydrate metabolism, alcohol intake can cause hypoglycemia, can reduce hepatic glucose production, and may also have a diabetogenic effect, inhibiting insulin secretion. In addition, alcohol interferes with the metabolism of lipids, leading to an increase of triglycerides and secretion of VLDL by the liver, as well as an increased protein turnover and negative nitrogen balance[86]. Vitamin deficiency is frequent in alcoholics due to their decreased absorption, impaired ability to store fat-soluble vitamins, and alterations in the vitamins' metabolism and activation. A caloric intake of 25-35 kcal and 1-1.5 g of proteins per kg body weight can be recommended as a daily nutritional intake in alcoholic patients. A daily vitamin and mineral supplementation is advisable in most of these individuals[94].

Level of evidence: III

Management of Alcohol Use Disorders

Instruments for the Evaluation of Alcohol Intake

Alcoholic unit: definition

The daily alcohol intake assessment can be estimated using an arbitrary unit named Alcoholic Unit (AU) or Drink. This corresponds to 12-13 g of pure ethanol contained in a 125 ml glass of wine, in a 330 ml of beer can, or in a 40 ml shot of spirits[95,96].

Modality of history taking

An adequate history is essential for the evaluation of alcohol consumption and abuse. Many patients and their relatives may show a natural reticence on this subject and are prone to hide or minimize the amounts of alcohol consumed[97]. Therefore, it may be useful to focus on the so-called indirect factors, such as road accidents, domestic accidents, frequent job changes, frequent emergency room admittance, withdrawal of driving license, legal problems (arrests for insult, fighting, sexual abuse), aggressive behavior, and violence against children that can give rise to the suspicion of alcoholic abuse in subjects who are reluctant to admit it[98-100]. Clinical data collection should include the self-reported daily alcohol consumption, expressed in AU, the types of alcoholic beverages, the age of first regular drinking, the alcohol consumption modalities, the drinking time and the investigation of family members.

These data can be used to distinguish different drinking patterns as shown in Table II[101,102].

Level of evidence: I
Strength of recommendations: A

Alcohol abuse/dependence

Criteria for the diagnosis of substance dependence, including alcohol, are codified in the 10th edition of the International Classification of Diseases, approved by the WHO in 1990 (ICD-10)[103-105].

There is no evidence from randomized clinical trials or cohort studies to support this, but this recommendation has been supported by the scientific consensus of experts.

More specific criteria for the diagnosis of alcohol dependence and abuse are detailed in the IV edition of the Diagnostic and Statistical Manual of mental disorders released by the American Psychiatric Association (DSM-IV)[106].

Level of evidence: VI
Strength of recommendations: A

Questionnaires to detect alcohol dependence or abuse

Clinicians should discuss alcohol use with their patients, and any suspicion of possible abuse or excess should prompt the use of a structured questionnaire and further evaluation[107-109].

This recommendation is based not on randomized clinical trials or cohort studies but on case series without a control group. Nevertheless, the use of questionnaires to detect alcohol dependence/abuse is strongly recommended and has

Table II. Characteristics of the different drinking patterns.

1. Abstemious: a person who does not take alcoholic beverages
2. Abstinent: a person who, for whatever reason, has stopped drinking alcohol
3. Subject with low-risk consumption: In recent decades the so-called low-risk amount is gradually decreased. If still many scientific sources speak of an alcohol consumption of less than 20 g for adult women and 40 grams for adult men, the U.S. Food Guidelines (2010) and the American Institute for Cancer Research (2007) establish the following cut-off:
   - 1 U.A. (10-12 g of alcohol) per day for adult women and the elderly
   - 2 U.A. (20-25 g of alcohol) per day for a man
4. Subject with hazardous consumption: a consumption level or drinking mode that may create a hazard in case of persistence of these habits.
   The WHO describes it as an average daily consumption of more than 20 g of pure alcohol for women and more than 40 g for men.
5. Subject with harmful consumption (this category also includes binge drinking): The harmful use is defined as "a mode of alcohol consumption that causes harm to health, both physical (such as cirrhosis) or mental (such as depression by alcohol intake)" (WHO 1992). WHO has adopted as the definition of harmful consumption average daily intake of 40 g of alcohol for women and more than 60 g for men.
6. Subjects with alcohol dependence: a set of physiological, behavioral and cognitive events in which alcohol consumption plays an increasing priority than previously important habits.

U.A. = Alcohol Unit. WHO = World Health Organization

been supported by a good quality scientific consensus of experts.

Level of evidence: V
Strength of recommendations: A

Various questionnaires have been proposed to detect alcohol dependence or abuse (Table III).

a) The Lifetime Drinking History measures the total amount of alcohol consumption within the lifetime of the patient[107] (http://www.emcdda.europa.eu/html.cfm/index4163EN.html).
b) The CAGE (Cut-down Annoyed Guilty Eye opener) aims to assess the consequences of alcohol intake rather than its magnitude in relation to the lifestyle of the subject[110,111] (http://pubs.niaaa.nih.gov/publications/AssessingAlcohol/InstrumentPDFs/16_CAGE.pdf).
c) The AUDIT test (Alcohol Use Disorders Identification Test): is a questionnaire composed of 10 items[112] proposed by the World Health Organization (WHO) that aims to identify persons with a significant alcohol consumption[113] (http://www.testandcalc.com/etc/tests/audit.asp).

The AUDIT C is a simplification of the AUDIT, using only the three questions on alcohol consumption. It seems more effective than the full version, with a sensitivity of 54-98% and a specificity of 57-93%, but according to some authors, its focus is on alcohol dependence but not on hazardous consumption makes it less effective than AUDIT in female patients[114] (http://www.ewashtenaw.org/government/departments/wcho/ch_auditc.pdf).

d) The tests described are reliable but rather complex; in the areas of emergency medicine and the emergency room, more agile tests are required to enable faster screening, such as the FAST (Fast Alcohol Screening Test) (http://www.effectivepi.co.uk/files/FAST%20&%20other%20AUDIT%20questions_EPI%20version%20 Mar%2009.pdf)[115] and the Paddington Alcohol Test, developed in Anglo-Saxon environments[116] (http://www.sips.iop.kcl.ac.uk/documents/gnr/PAT.pdf).

Biochemical tests

For patients with a history of alcohol abuse or excess and evidence of liver disease, further laboratory tests should be performed to exclude other etiologies and to confirm the diagnosis[117].

There is no evidence from randomized clinical trials or cohort studies to support this recommendation. Nevertheless, the biochemical tests to evaluate alcohol intake are strongly recommended and are supported by case series and good quality scientific consensus of experts.

Level of evidence: V
Strength of recommendations: A

Table III. Instruments for the evaluation of alcohol intake.

Clinical data collection		
Questionnaires to detect alcohol dependence or abuse		LDH
		CAGE
		AUDIT
		FAST
		PAT
Biochemical tests	Nonspecific tests	γGT
		MCV
		AST
		Uric acid, triglycerides, urea
	Specific markers	Indicators of recent use (blood and urine alcohol concentration, 5-hydroxyindoleacetic/5-hydroxy triptofolic acid ratio)
		Indicators of chronic use (carbohydrate-deficient transferring, Hb A, sialic acid, β-hexosaminidase, ethyilglucuronide, fatty acid ethyl esters)

LDH = Lifetime Drinking History; CAGE = Cut-down Annoyed Guilty Eye opener; AUDIT = Alcohol Use Disorders Identification Test; FAST = Fast Alcohol Screening Test; PAT = Paddington Alcohol Test; γGT = Gamma Glutamyl Transpeptidase; MCV = Mean Corpuscular Volume; AST = Aspartate aminotransferase; Hb = Hemoglobin.

Biochemical tests have been considered to be less sensitive than questionnaires in screening for alcohol abuse[118] but may be useful in identifying relapse[109]. We can distinguish between markers of chronic and recent alcohol intake using nonspecific and specific tests (Tables IV and V).

Follow up and Treatments

Protracted behavior modification, cognitive behavioral therapy, psychological counselling, and mutual support groups (e.g., Alcoholic Anonymous) have been considered the most effective long-term treatments.

The Self Help Groups (SHG) are small groups of people (6 to 8) who meet, driven by a need to share, to overcome a problem and to achieve change through mutual aid[119]. The operation of SHG is governed by shared norms and accepted by members of the groups at the time of entry (confidentiality, equality, neutrality of the setting, respect, acceptance and privacy). For those suffering from mental illness, there are weekly meetings, including meetings for the family once every 15 days for the entire last hour and a half. Each group is coordinated by two facilitators, who are supervised by a professional who attends refresher courses in a program of lifelong learning.

In Italy, there is a territorial service (Ser. T.) that takes care of preventing, treating and rehabilitating states of addiction, particularly for psychotropic substances and alcohol. The Ser. T. helps those who use drugs or alcohol to quit, give advice on drugs and alcohol to citizens, families, schools, public institutions, private institutions and citizens and spreading a culture of life without legal or illegal drugs.

Pharmacotherapy of Alcoholism

Disulfiram

A recent review showed that disulfiram was an effective therapeutic tool in all clinical studies published from 2000 to 2008 and suggested that supervised low-dose disulfiram (not more than 100 mg/day) will achieve the highest success when it is carefully integrated into psychotherapeutic alcoholism therapy[120-122].

Level of evidence: I
Strength of recommendation: B

Naltrexone

A meta-analysis involving a total of 2861 subjects in 24 randomized clinical trials showed, for short-term treatment, a more sig-

Table IV. Markers of recent intake of alcohol[109, 118].

Marker	Biological matrix	Normal value	Sensibility	Specificity	Persistence time	Reliability
Ethanol	blood, urine, breath, saliva	0.1 g/L	100	95-100	8-10 h	++++
Methanol	blood, urine, breath	< 0.1 g/L	< ethanol	<ethanol	10-15 h	+---
5-HTOL/5-HIAA	urine	20 pnc/nmol	60-80	90-95	20-25 h	++--
Ethylglucuronide	urine, serum, keratin	Absent	high	high	25 h blood 90 h urine 3-6 months keratinic matrix	+++-
Ethyl sulphate	urine, serum, keratinic matrix	Absent	medium-high	high	25-30 h blood 90-100 h urine 3-6 months keratinic matrix	+---
FAEE	urine, serum, keratinic matrix	< 0.8 ng/mg	low	low	15-20 h blood 3-6 months keratinic matrix	++--

5-HTOL/5-HIAA = 5-hydroxytryptophol/5-hydroxyindole-3-acetic acid ratio. FAEE = Fatty Acid Ethil Esters.

nificant role of naltrexone in decreasing relapses than in decreasing the return to drinking, suggesting that naltrexone should be accepted as a short-term treatment for alcoholism[123]. Moreover, a more recent meta-analysis revealed that oral naltrexone is effective in reducing relapse in heavy drinking but less effective in enhancing abstinence[124,125].

Level of evidence: I
Strength of recommendation: A

Acamprosate

Acamprosate is a functional glutamate antagonist, the mechanism of action of which is not completely known. The clinical efficacy of acamprosate in decreasing alcohol craving and in maintaining abstinence has been robustly documented in meta-analyses of available studies[126,127]. The directions for acamprosate are two 333 mg tablets, 3 times a day. A recent meta-analysis of twenty-four randomized clinical trials with 6915 participants showed that, compared to placebo, acamprosate significantly reduced the risk of any drinking and significantly increased the cumulative abstinence duration. Diarrhea was the only side effect that was more frequently reported under acamprosate than the placebo. Acamprosate was shown to be safe in patients with hepatic impairment, while a dose reduction is recommended in patients with renal impairment[128]. However, to date, no specific studies on the efficacy and safety of acamprosate in alcohol-dependent patients affected by alcoholic liver disease (ALD) have been conducted.

Level of evidence: I
Strength of recommendation: B

Gamma-hydroxybutyric acid (GHB)

Gamma-hydroxybutyric acid (GHB) is a short-chain 4-carbon fatty acid that is particularly present in the hypothalamus[129]. GHB shares several similarities with the pharmacologic profile of ethanol[130], and short-term studies in which GHB was administered to humans have shown that it can suppress the alcohol withdrawal syndrome with an efficacy similar to that of diazepam and chlormethiazole[131,132] GHB also increases the percentage of abstinent days, reduces the number of daily drinks, and reduces craving[133]. GHB is well tolerated, with side effects including dizziness, hyporeflexia and somnolence. Up to 30-40% of alcohol-dependent patients do not respond to GHB treatment, and the short half-life of the drug (approximately 2 h) is considered a possible cause. In these patients, the increased dose fractioning

Table V. Markers of chronic intake of alcohol[109, 118].

Marker	Biological matrix	Normal value	Sensibility	Specificity	Persistence time	Reliability
CDT	Blood	<2.6-4% asialo+disialo <1.27% disialo/tetrasialo	60-90	>90	2 weeks	+++-
HbA	blood	<9 mmol/l ach.tot	?	60-70	4 weeks	++--
Sialic acid	blood	52-73 mg/dl	45-60	70-80	1-4 weeks	++--
β-hexosaminidase (β-HEX)	urine, blood, keratinic matrix	< 6.2 U/L	High	High	4-5 days	+---
Etilglucuronide	urine, blood, keratinic matrix	Absent	medium-high	High	25-30 h blood 90-100 h urine 3-6 month keratinic matrix	+---
Fatty Acid Ethyl Esters (FAEE)	urine, blood, keratinic matrix	<0.8 ng/mg	Low	low	15-20 h blood 3-6 month keratinic matrix	++--

seems to be able to cause a significant reduction in craving, increasing the therapeutic efficacy and decreasing the risk of abuse[134,135].

Level of evidence: III
Strength of recommendation: C

Baclofen

Baclofen is a selective GABA B receptor agonist. In large trials vs placebo, the results showed baclofen's efficacy in reducing alcohol intake, craving scores, and state anxiety, as well as in increasing cumulative abstinence duration[136]. Baclofen was also reasonably tolerated, and no serious adverse events were reported. The most common side effects were sleepiness, tiredness, and vertigo, which tended to resolve within 1-2 weeks of drug treatment. All of the studies reported above tested baclofen at a dose of 10 mg t.i.d. In a more recent study, the effect of baclofen 20 mg t.i.d. was significantly higher than that of baclofen 10 mg t.i.d., showing a dose–effect relationship. Both doses of baclofen were well tolerated.

Level of evidence: I
Strength of recommendation: B

Topiramate

In different studies, topiramate was superior to placebo in improving physical health outcomes and measures of psychosocial functioning[137], with a greater efficacy than placebo in improving the quality of life, decreasing the severity of alcohol dependence, and reducing the detrimental consequences associated with heavy drinking.

Level of evidence: I
Strength of recommendation: B

Fluoxetine, other Serotonin Reuptake Inhibitors and Ondansetron

Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), seems to act through GABA-ergic action, as well as through serotoninergic mechanisms; it is administered at a dose of 20 mg/day for the first 2 days, with a subsequent dose of 60 mg/day, taking care to watch for the possible occurrence of maniac reactions[138]. Recent studies have shown that the efficacy of fluoxetine in alcoholic patients is affected by depression. At a dose of 20 mg/day for the first 2 weeks then 40 mg/day if necessary, fluoxetine has proven to be effective in reducing depressive symptoms and alcohol consumption in these patients[139]. Its efficacy, however, seems to decrease in alcoholic patients without significant mood disorders. There are some contrasting data on the efficacy of sertraline and citalopram (SSRI agents). It seems that SSRIs might be useful in late-onset alcoholics, while ondansetron at a dose of 0.5-4 mg divided into two daily doses for 6 weeks could be effective in early onset alcoholics. Ondansetron (5HT3 receptor antagonist) is able to increase dopamine levels through its blocking action on

the 5HT3 receptor. This drug seems to be effective in reducing cravings and alcohol intake in early onset alcoholics. Moreover, recent data showed the efficacy of ondansetron in some genetic subtypes of alcoholic patients[140].

Level of evidence: III
Strength of recommendation: C

Medical Management of Alcohol Dependence in Patients with ALD

In addition to dietary supplement therapy, several drugs have been tested to improve survival in patients with ALD, including corticosteroids, propylthiouracil, S-adenosyl-L-methionine, infliximab and pentoxifylline[141].

Regarding the central role of alcohol-mediated oxidative damage, different efforts to identify an effective anti-oxidant therapy, have been made.

The role of the anti-oxidant pentoxifylline has been explored in a single well-designed, controlled trial[142], which found that treatment with pentoxifylline is associated with improved in-hospital survival in patients with severe alcoholic hepatitis. In practice, its administration in patients with severe disease could be considered, especially if there are contraindications to steroid therapy.

Level of evidence: II
Strength of recommendation: B

Treatments with anti-TNF-α therapies, such as Infliximab[143] and Etanercept[144], were associated with increased risks of infection and death in two randomized controlled trials, and so they are not recommended.

Level of evidence: II
Strength of recommendation: D

The anti-inflammatory properties of corticosteroids seem to contribute to the reduction of short-term mortality in selected patients with severe alcoholic hepatitis, as observed in multiple randomized controlled trials[145,146]; consequently, their administration could be considered in severe patients, if there are no contraindications.

Level of evidence: I
Strength of recommendations: A

Independent of the stage of ALD, abstinence from alcohol is the cornerstone of management because medical and surgical treatments for ALD have limited success when drinking continues. Accordingly, total alcohol abstinence can improve the histology and/or survival of individuals with ALD and the clinical outcomes of all stages of ALD[147].

Psychological approaches and counselling are essential components of therapy to promote abstinence in these patients. However, the efficacy of group and supportive psychotherapy is relatively low when used as a monotherapy (15-39%). As reported above, at present, several medications have been found to be able to reduce alcohol craving and, consequently, to increase abstinence, preventing alcohol relapse. However, trials investigating anti-craving medications typically exclude individuals with high levels of transaminases and/or advanced liver disease, as they are concerned that these medications might worsen the liver disease. In fact, naltrexone is contraindicated in patients with liver disease due to its hepatic metabolism and reports of medication-related hepatic injury. Acamprosate may induce hyperammoniemia; topiramate affects liver function and may also induce hyperammoniemia.

In the last few years, growing evidence suggests a role for baclofen in the management of ALD patients; at present, baclofen is the only drug tested in alcohol-dependent patients affected by liver cirrhosis or acute alcoholic hepatitis. Baclofen showed a significant effect, compared to placebo, in reducing alcohol intake and craving. In conclusion, baclofen, because of its anti-craving action and safety and because of the need for alcohol abstinence both before and after OLT, could have an important role in the treatment of alcohol-dependent patients with advanced liver disease, including those needing liver transplantation (OLT).

Conclusions

In clinical practice, it is important to recognize alcohol abuse. A thorough clinical history for the evaluation of alcohol consumption and abuse in conjunction with a number of available questionnaires, are effective for detection alcohol dependence or abuse. Biochemical tests (nonspecific and specific) have been considered to be less sensitive than questionnaires in screening for alcohol abuse but may be useful in identifying relapse. Understanding the effects of alcohol on the digestive system as well as the underlying pathogenic mechanism(s) is crucial for correct management of alcohol-related disorders.

Protracted behavior modification, cognitive behavioral therapy, psychological counselling, and mutual support groups have been considered

the most effective long-term treatments for alcoholism. Several drugs that are able to interfere with the neurotransmitters involved in craving mechanisms have been studied with regard to their ability to increase abstinence and to prevent relapse. Collaborative initiatives between clinicians and other specialists are warranted in order to solve the problem of alcohol addiction.

Conflict of Interest

All authors have no interests, including personal or financial interests or connections, direct or indirect, or any other situations that could raise questions of bias in either the reported work or the conclusions, implications, or opinions stated.

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