Alcohol Prevention Day

XVII EDIZIONE
16 maggio 2018

Istituto Superiore di Sanità, Aula Pocchiari
Roma, Viale Regina Elena 299

APRILE MESE DI PREVENZIONE ALCOLOGICA

organizzato da:

Osservatorio Nazionale Alcol
Centro Nazionale Dipendenze e Doping

WHO Collaborating Centre
for Research and Health Promotion on Alcohol and
Alcohol-related Health Problems

In collaborazione con:

Ministero della Salute

e con:
Società Italiana di Alcologia - SIA
Associazione Italiana Club Alcologici Territoriali - AICAT
Eurocare

Position Paper/ Linee Guida SIA condivise

Gianni Testino

Centro Alcologico Regionale Ligure

ASL3

c/o Ospedale Policlinico San Martino, Genova

Società Italiana di Alcologia

Linee Guida / Position Paper SIA

Alcol e problemi alcol correlati. Indirizzi generali per l'organizzazione di base e orientamento delle offerte
Alcologia 2011; 11: 43-8

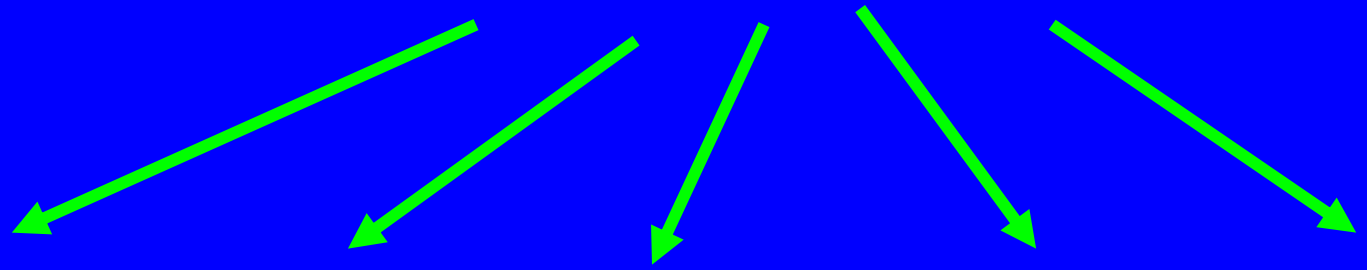
Gestione della intossicazione alcolica acuta, in press

Alcohol use disorders and liver transplantation, in press

Patologia delle addiction: è necessario un cambiamento, in press

Alcohol use disorders: prevention, diagnosis, treatment and rehabilitation

CONSUMO DI ALCOL



Fegato
Pancreas

Sistema Nervoso

-App. Cardio-Vascolare
-App. Digerente
-Sist. Emopoietico

-Stato Nutrizionale
-App. Immunitario
-Cancerogenesi
-Sist. Endocrino
-App. Riproduttivo
-App. Respiratorio
-S. Feto-Alcolica

< Performance
-< Qualita' di vita
<Aspettativa di vita

ALCOHOL

Fatty Liver

Alcohol Hepatitis/Fibrosis

Cirrhosis

Hepatocellular Carcinoma

Chronic Pancreatitis

Parotid Hypertrophy

Glossitis

Stomatitis

Gastro-Esophageal Reflux

Mallory-Weiss Syndrome

Chronic Gastritis

Erosive Hemorrhagic Gastritis

Delayed Gastric Emptyimg

Malabsorption

Reduce Transit Time

Carcinogenesis*

***Upper Aero-Digestive Tract, Colon, Rectum, Breast, Liver, Pancreas**

Testino G, Hepato-Gastroenterol 2008

ALCOLOGIA COINVOLTA IN NUMEROSE DISCIPLINE MEDICHE INTERNISTICHE

20% dei ricoveri ospedalieri

10% dei ricoveri i terapia intensiva

Complicanze post-chirurgiche

Importante fattore di trapianto d'organo

- **Non percepito il problema alcologico**

- **Se percepito non affrontato in modo adeguato**

- **Etica**

UNA NUOVA RIVOLUZIONE BASALIANA?

40-70% delle prime manifestazioni psicotiche in soggetti consumatori di alcol e/o sostanze

Alcol e/o sostanze slatentizzano patologie psichiatriche

Interazione farmacologica

Riduzione età media di soggetti polidipendenti e manifestazioni psicopatologiche

Table 1. The fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for the framing of patients with alcohol use disorder (AUD).

1.	Alcohol is often taken in larger amounts or over a longer period than was intended.
2.	There is a persistent desire or unsuccessful efforts to cut down or control alcohol use.
3.	A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects.
4.	Craving, or a strong desire or urge to use alcohol.
5.	Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home.
6.	Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol.
7.	Important social, occupational, or recreational activities are given up or reduced because of alcohol use.
8.	Recurrent alcohol use in situations in which it is physically hazardous.
9.	Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.
10.	Tolerance, as defined by either of the following: (a) A need for markedly increased amounts of alcohol to achieve intoxication or desired effect; (b) A markedly diminished effect with continued use of the same amount of alcohol.
11.	Withdrawal, as manifested by either of the following: (a) The characteristic withdrawal syndrome for alcohol (refer to criteria A and B of the criteria set for alcohol withdrawal); (b) Alcohol is taken to relieve or avoid withdrawal symptoms.

all the criteria in Table 1). The presence of two or three symptoms indicate a mild disorder, four or five symptoms a moderate one, and six or more symptoms a severe disorder. Notably, DSM-5 removes "legal problems" between the diagnostic criteria adding the craving [11].

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed.; American Psychiatric Association: Washington, DC, USA, 2013; pp. 154–196.

ASSOLUTA SPECIFICITA' DEL SETTORE ALCOLOGICO

L'alcologia è una «disciplina « che raccoglie elementi della salute pubblica, della medicina interna, della neurologia, della tossicologia e anche della psichiatria

L'inserimento dell'alcologia nell'area psichiatrica rimanda prettamente ad un problema di patologia quello che ha a che fare con lo stile di vita, con scelte e comportamenti

DSM-5: continuum da lieve a grave

(per gestione «continuum» professionalità specifica/dedicata)

ABSOLUTE BEST:

abstension: the best of the best

What is the best model for the treatment of alcohol dependence?

What is the best available model for treating the individual patient now, in the current phase of his/her disease, fully taking into account the specific clinical, personal, family, and environmental conditions?

What is the realistic target, allowing for these particular constraints?

The relative best !!!

ETICA E DISTURBI DA USO DI ALCOL

Astensione/ *Riduzione Consumo*

Resistenza alla terapia psico-sociale/auto aiuto (no risorse)

Rifiuta astensione assoluta (40-60%)

Migliore gestione assistenziale

Miglioramento salute della famiglia con eventuale coinvolgimento

Accesso alla terapia disintossicante

Migliore valutazione co-morbilita' psichiatrica

Migliore gestione problematiche internistiche

Maggiore possibilità di inserimento nei gruppi di auto-aiuto

«A pragmatic approach should be adopted towards patients who initially reject abstinence as a treatment goal»

Connor et al, Lancet 2016

REAL PRACTICE

Riduzione del consumo?

Raggiungere il sommerso? Raggiungere chi chiede aiuto, ma ha scarse risorse? Non accetta o non può raggiungere un immediata astensione?

Accettato per brevi periodi (4-6 mesi!)

Se diventa il metodo:

- **si uccide la speranza e si tradisce chi chiede aiuto**
- **si agisce come alleati della dipendenza e si induce la cronicizzazione**
- **si favorisce la manipolazione del «dipendente», il suo vittimismo con il rischio di un deleterio compromesso**

Table 4. Treatment goals, as proposed in the UK NICE guidelines (2011) [108] also adopted by the German guidelines (2016) [112]

1. In the initial assessment in specialist alcohol services of all people who misuse alcohol, agree the goal of treatment with the service user. Abstinence is the appropriate goal for most people with alcohol dependence, and people who misuse alcohol, and have significant psychiatric or physical comorbidity (e.g., depression or alcohol-related liver disease). When a service user prefers a goal of moderation but there are considerable risks, advise strongly that abstinence is most appropriate, but do not refuse treatment to service users who do not agree to a goal of abstinence.
2. For harmful drinking or mild dependence, without significant comorbidity, and if there is adequate social support, consider a moderate level of drinking as the goal of treatment unless the service user prefers abstinence or there are other reasons for advising abstinence.
3. For people with severe alcohol dependence, or those who misuse alcohol and have significant psychiatric or physical comorbidity, but who are unwilling to consider a goal of abstinence or engage in structured treatment, consider a harm reduction program of care. However, ultimately the service user should be encouraged to aim for a goal of abstinence.
4. When developing treatment goals, consider that some people who misuse alcohol may be required to abstain from alcohol as part of a court order or sentence.

UK NICE guidlines, 2011

German Guidlines, Eur Addict Res 2017

Table 5. Clinical guidelines issued by the US National Institute on Alcohol Abuse and Alcoholism (NIAAA 2005) [114]

"…Abstaining is the safest course for most patients with alcohol use disorders. […] Still, it is best to determine individualized goals with each patient. Some patients may not be willing to endorse abstinence as a goal, especially at first. If an alcohol-dependent patient agrees to reduce drinking substantially, it is best to engage them in that goal while continuing to note that abstinence remains in the optimal outcome."

Table 6. Guidance paper of the European Medicines Agency, 2010 [1]

"As the key secondary endpoint efficacy should also be evaluated in terms of responders, reflecting an expected significant improved health outcome on an individual patient level. This could be done by evaluating the proportion of subjects with a 50, 70, and 90% reduction in alcohol consumption as well as the proportion of patients achieving maintained abstinence. Another option would be evaluating the proportion of subjects with a significant categorical shift in WHO risk levels of drinking (i.e., proportion of patients with change of consumption to baseline from very high risk to at least medium risk level and change from high risk to at least low risk level, as well as the proportion of patients with full abstinence)."

National Institute on Alcohol Abuse and Alcoholism, 2005

European Medicines Agency Guideline, 2010

RISCHIO ALCOL CORRELATO: UN CONTINUUM

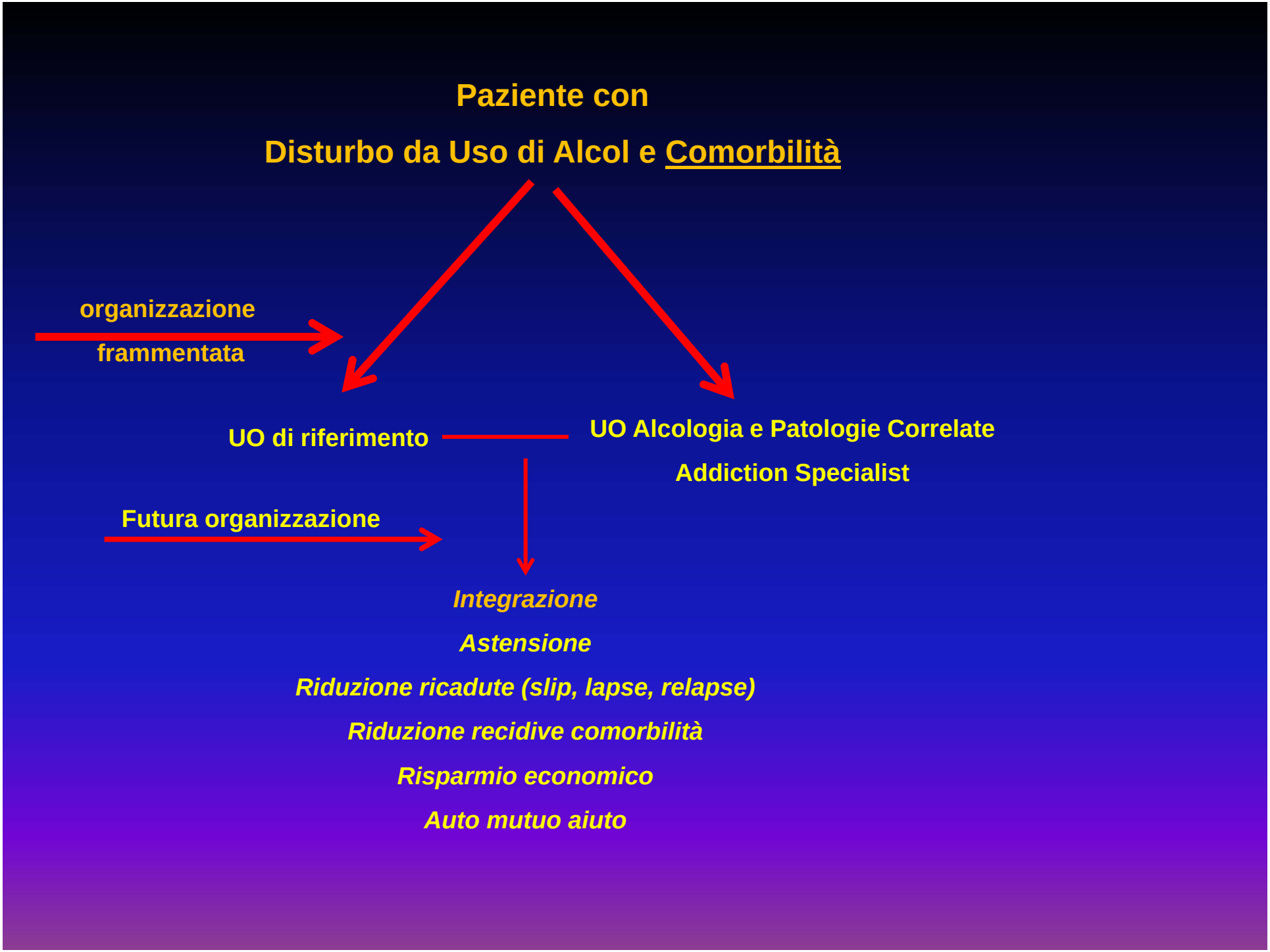
Impossibile verificare le modifiche delle abitudini di consumo o lo spostamento della persona da una categoria di medio rischio a quella di alto rischio

1) Diagnosi precoce e trattamento delle PPAC (nella prima fase non sottovalutare riduzione del consumo)

2) Creare rete d'identificazione precoce del rischio e intervento breve

3) Formalizzare e garantire la formazione specifica sull'IPIB per il settore di Primary Health Care

4) Sviluppo associazioni di auto mutuo aiuto


Paziente con
Disturbo da Uso di Alcol e Comorbilità
organizzazione
frammentata
UO di riferimento
UO Alcologia e Patologie Correlate
Addiction Specialist
Futura organizzazione
Integrazione
Astensione
Riduzione ricadute (slip, lapse, relapse)
Riduzione recidive comorbilità
Risparmio economico
Auto mutuo aiuto

TAILORED THERAPY

patient characteristics

Type of alcoholic patients (Cloninger or Lesch type)

Lesch's type III and IV: best treatment with Naltrexone

Lesch' s type I annd II: best treatment with Acamprosate

Cloninger type I: best treatment with Acamprosate

Cloninger type II: best treatment with Ondasentron plus NTX

Type of craving (reward, relief, obsessive)

Gene polymorphism (OPMR1, GATA, 5-HTT, …)

Other drugs addiction

Psychiatric comorbidities

Internistic comorbidities (i.e. hepathopaty)

Self Help (AA or CAT)

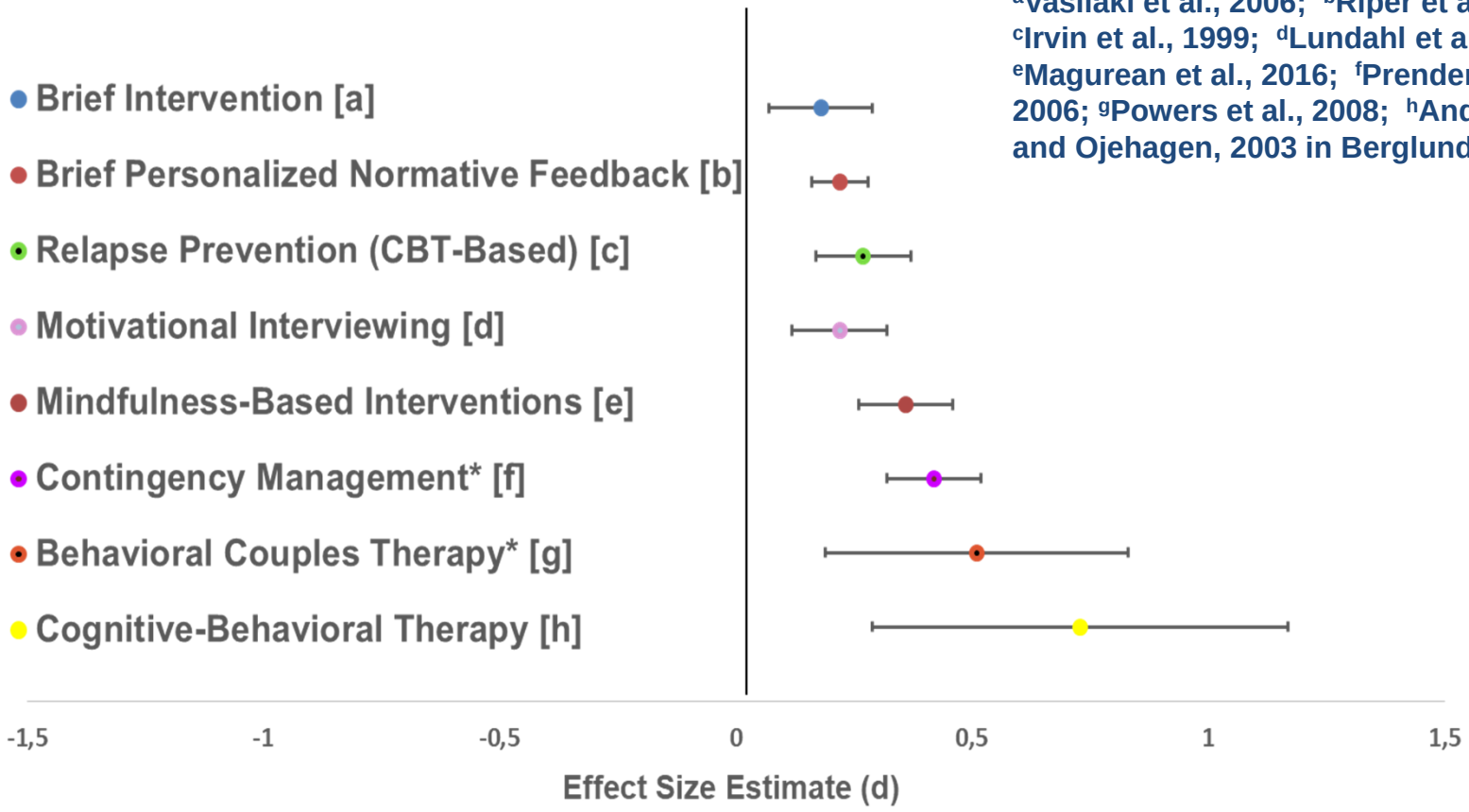
Effective Anticraving Medications for Alcohol Dependence

Medication	Mechanism of Action
Naltrexone (Nalorex® and Vivitol®); Nalmefene (Selincro®)	Mu opioid receptor inhibitor ?OPRM1 (label)
Acamprosate (Campral®)	Glutamate receptor modulation (label)
Ondansetron (Zofran®)	Serotonin- 3 receptor antagonist (off-label) Type B/SERT & 3-UTR
Sodium Oxybate (SO) (Alcover®)	GABA-B/ GHB agonist (label in Italy and Austria)
Topiramate (Topamax®)	GABA/Glutamate modulator Heavy current drinkers (off-label)
Baclofen (Lioresal® and Liofen®)	GABA-B antagonist (label in France) Alcohol dependent; Severe liver disease
Gabapentin (Neurontin®)	GABA analog (activity may involve interaction with voltage-gated calcium channel) (off-label)
Varenicline (Champix®)	Nicotinic receptor partial agonist (off-label)

Addolorato et al, Neuropsychopharmacol 2012

Alcohol Use Disorders

- **In AUD patients, behavioral therapies are essential components of treatment**



[a]Vasilaki et al., 2006; [b]Riper et al., 2009; [c]Irvin et al., 1999; [d]Lundahl et al., 2010; [e]Magurean et al., 2016; [f]Prendergast et al., 2006; [g]Powers et al., 2008; [h]Andreasson and Ojehagen, 2003 in Berglund et al., 2003

- **Pharmacotherapy is able to improve alcohol-related outcomes**

IARC; Lancet Oncology, November 2009

	Tumour sites for which there is sufficient evidence	Tumour sites for which there is limited evidence	Tumour sites for which there is evidence suggesting lack of carcinogenicity
Tobacco smoking	Oral cavity, oropharynx, nasopharynx, and hypopharynx, oesophagus (adenocarcinoma and squamous-cell carcinoma), stomach, colorectum,* liver, pancreas, nasal cavity and paranasal sinuses, larynx, lung, uterine cervix, ovary (mucinous)*, urinary bladder, kidney (body and pelvis), ureter, bone marrow (myeloid leukaemia)	Female breast*	Endometrium (postmenopausal*), thyroid*
Parental smoking (cancer in the offspring)	Hepatoblastoma*	Childhood leukaemia (in particular acute lymphocytic leukaemia)*	
Second-hand smoke	Lung	Larynx,* pharynx*	
Smokeless tobacco	Oral cavity, oesophagus,* pancreas		
Areca nut			
Betel quid with added tobacco	Oral cavity, pharynx, oesophagus		
Betel quid without added tobacco	Oral cavity, oesophagus*	Liver*	
Alcohol consumption	Oral cavity, pharynx, larynx, oesophagus, liver, colorectum, female breast	Pancreas*	Kidney, non-Hodgkin lymphoma
Acetaldehyde associated with alcohol consumption	Oesophagus,* head and neck*		
Chinese-style salted fish	Nasopharynx	Stomach*	
Indoor emissions from household combustion of coal	Lung		

*New sites.

Table: Evidence for carcinogenicity in humans of Group 1 agents assessed

IARC; Lancet Oncology, November 2009

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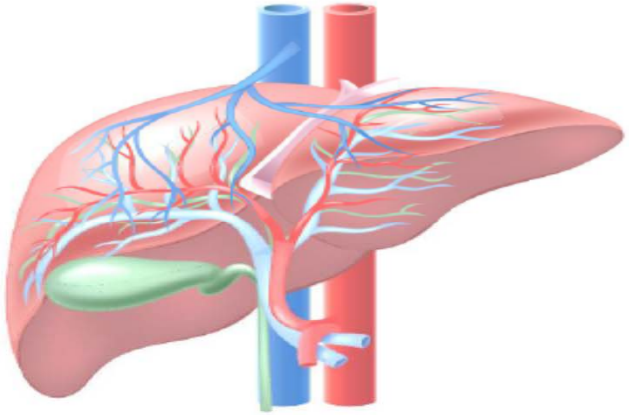
Table: Evidence for carcinogenicity in humans of Group 1 agents assessed

Asl3
Sistema Sanitario Regione Liguria

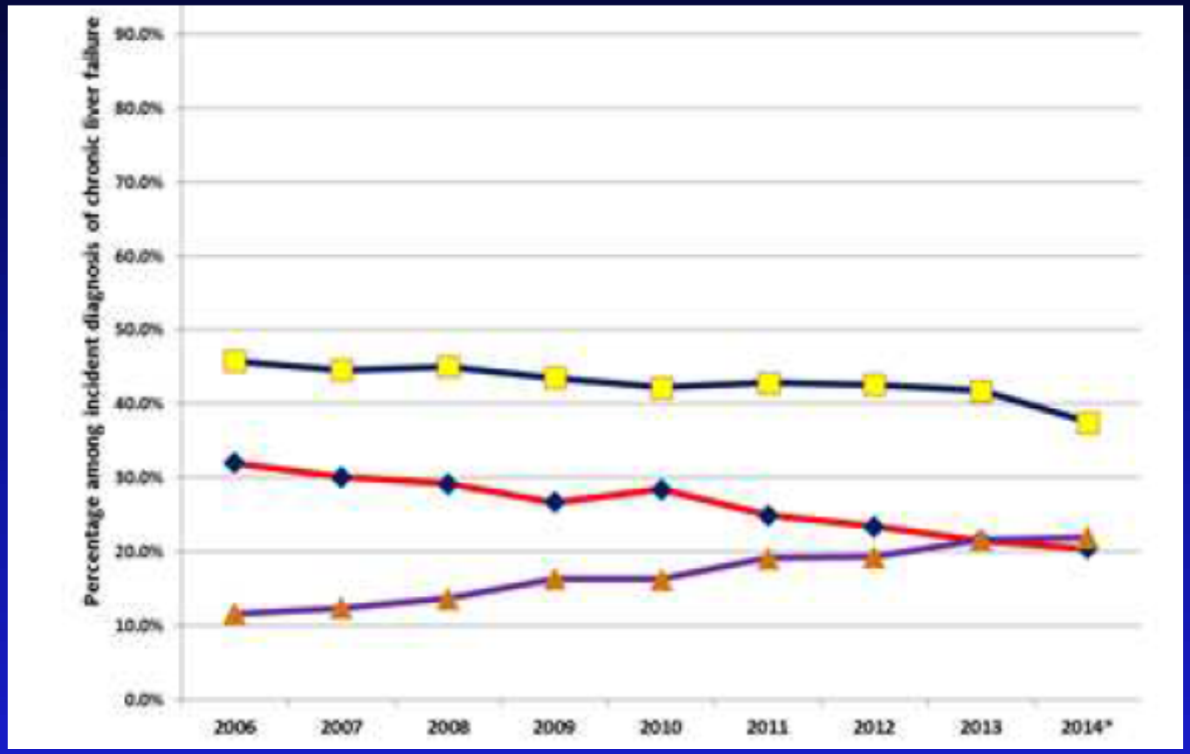
ALCOHOL USE DISORDERS (AUDs) E TRAPIANTO DI FEGATO

Position paper della Società Italiana di Alcologia (SIA)

Per lo sviluppo, il management e l'aggiornamento di linee guida e di buone pratiche cliniche per il trapianto di fegato conseguente a disturbi da uso di alcol
Integrazione Ospedale-Territorio

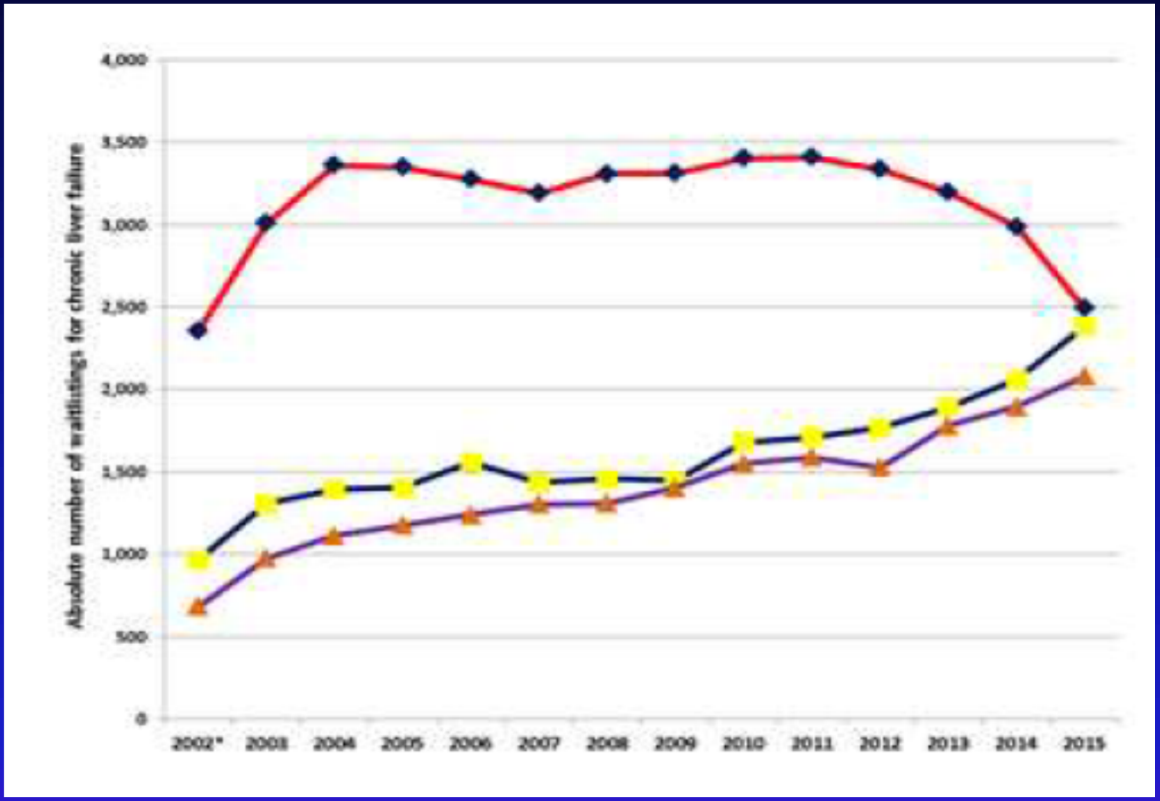


Diagnosis of distribution among patients with an incident diagnosis of compensated cirrhosis



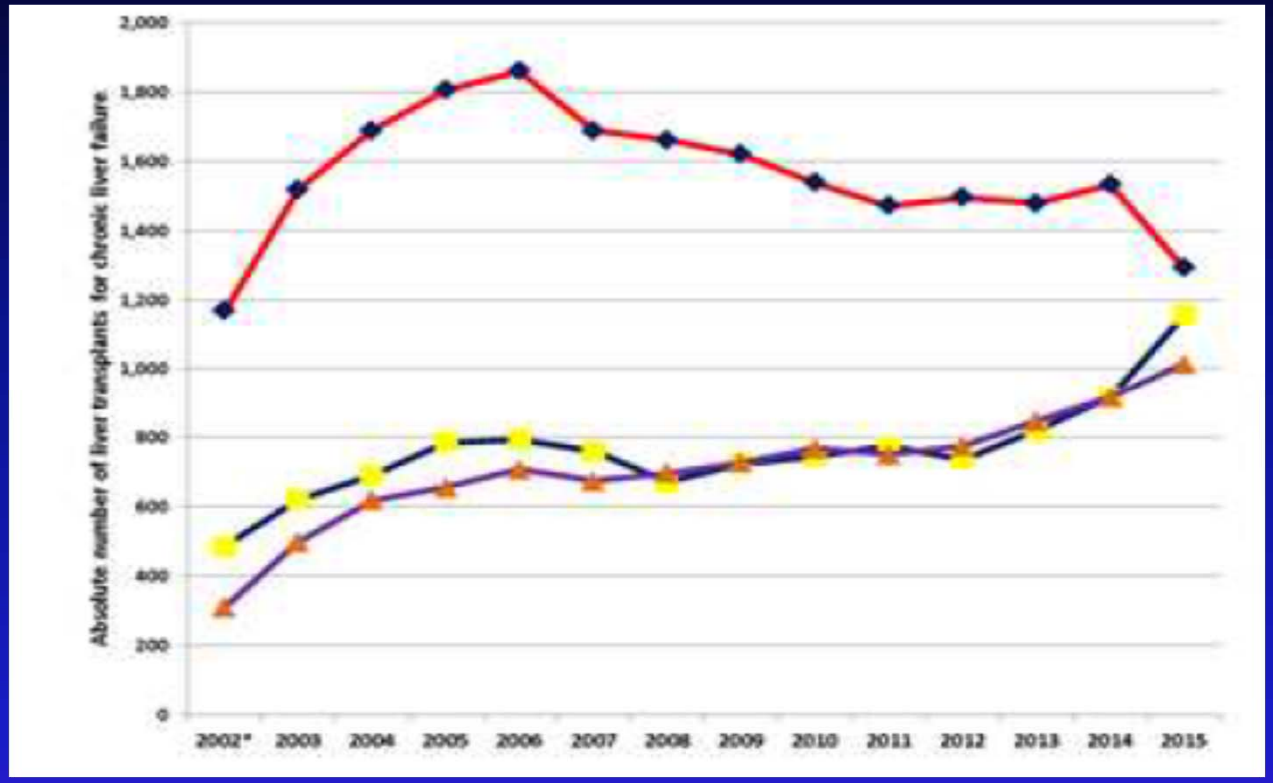
Goldberg et al, Gastroenterology 2017

Absolute number of new wailisting for chronic liver failure by etiology of liver disease



Goldberg et al, Gastroenterology 2017

Absolute number of liver transplants for chronic liver failure by etiology of liver disease



Goldberg et al, Gastroenterology 2017

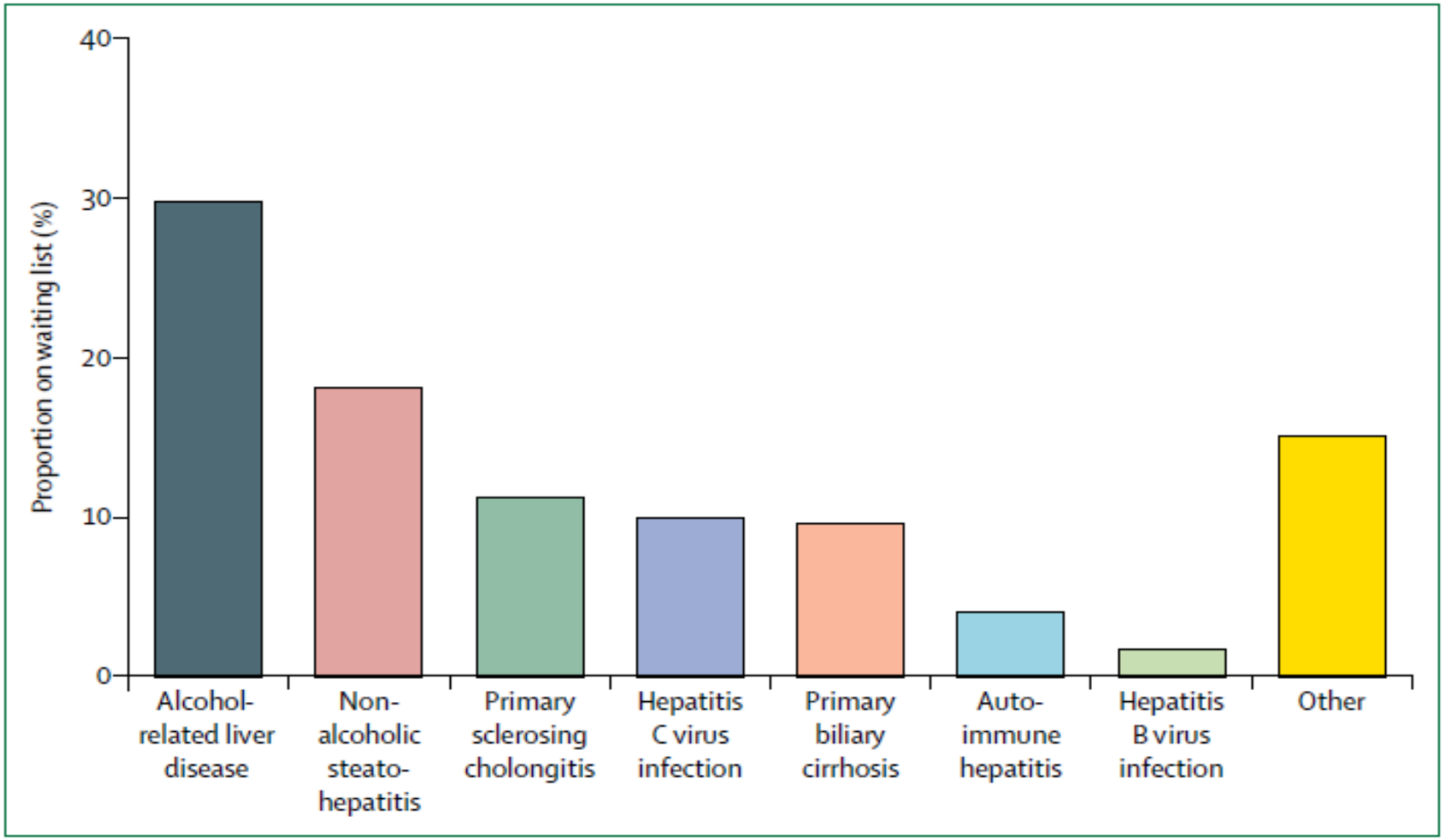


Figure 6: Causes of liver disease in patients on liver transplantation waiting list as of January, 2017

Williams et al, The Lancet, Vol 391 March 17, 2018

TRAPIANTO DI FEGATO ALCOL CORRELATO

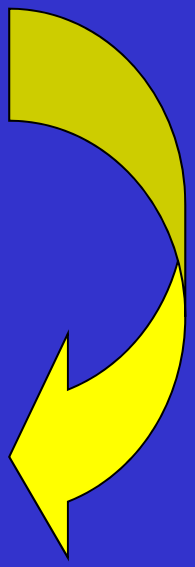
Comorbilità Internistica: neoplasie, cardiopatia, neuropatia, nefropatia, pancreatite, pneumopatie ….

Possibile Comorbilità Psichiatrica

Astinenza (6 mesi ?)

PROBLEMI ETICI
TRAPIANTO DI FEGATO e ALCOL

- **Patologia “auto-inflitta”**
- **Opinione pubblica**
- **Difficoltà nel definire criteri predittivi di recidiva**
  - **» Rischio di scarsa “compliance”**



CARENZA DI DONATORI D’ORGANO

STUDIO HONG KONG

281 intervistati sulla utilità del Trapianto di Fegato

75%

per chi affetto da **malattia naturale**

ma non per chi presenta **malattia epatica autoinflitta**

Chang, Hong Kong Medical Journal 2006

Assessing priorities for allocation of donor liver grafts: survey of public and clinicians

,

Opinione:

- Il 17% di 1.000 persone intervistate tra la popolazione generale
- Il 40% di 200 medici di Medicina Generale
- Il 33% di 100 medici Specialisti in Gastroenterologia

riteneva che

"Il paziente con malattia epatica alcol correlata
è il candidato meno meritevole per il trapianto di fegato"

Neuberger J Br Med J 1998

EPATITE ALCOLICA ACUTA

La manifestazione clinica copre un largo spettro di segni e sintomi che vanno dall'ittero asintomatico a forme più severe caratterizzate dalla combinazione di encefalopatia, febbre, astenia, coagulopatia, leucocitosi

Wells JT, Liver Transplantation 2007

Mortalità a 30 giorni: 35-40% dei casi; a 6 mesi: 70% dei casi

Day CP, Liver Transplantation 2007; Burroughs AK, Int Hepatol 2012

Alcoholic Hepatitis and Liver Transplantation: Is an Abstinence of Six Months Necessary?

Gianni Testino and Paolo Borro

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To the Editor,

Forty-four percent of all deaths from liver disease are attributed to alcohol (1). Alcoholic liver disease (ALD) is the second most common diagnosis among patients undergoing liver transplantation (LT) in Europe and the Unites States. The outcome for patients transplanted for ALD is at least as good as that for most other diagnoses and better than that for HCV (2).

Forman *et al.* (3) evidenced a 5 year survival of 69.9% of HCV positive recipients and of 72% in HCV negative recipients transplanted for ALD. In HCV recipients, fibrosis/cirrhosis was present in 10-21% five years from LT. Reported rates of alcohol relapse ranged from 11.5-49%, although this fact was rarely considered a reason for graft failure in recipients with ALD. Graft dysfunction related to relapse ranged from 0 to 17%, although deaths related to relapse ranged from 0% to 5% (4). More recently, Tandon *et al.* (5) evidenced the risk of post-transplant problem drinking in 13% of cases. In this study there was no survival difference between problem drinkers and non-drinkers.

Alcoholic hepatitis (AH) is a clinical syndrome of jaundice and liver failure that generally occurs after decades of heavy alcohol use. The typical age of presentation is 40 to 60 years (6). The true incidence of AH is unclear. Its prevalence is around 20% among subjects who undergo liver biopsy and it is suspected in 10-35% of hospitalized alcoholics. Less severe forms of acute AH (AAH) frequently respond to alcohol abstinence, whereas the prognosis of severe AAH is poor; up to 40% die within 6 months. Cirrhosis co-exists in over 50% of cases and patients are at risk of variceal bleeding and hepatorenal syndrome (HRS) (7). Severe AAE non-responders to steroids have 6 months survival (approx. 25-30%) and in patients with HRS there is a 3-month mortality of more than 90% unless treated by LT (8-10).

In cases of severe AAH, LT is a therapeutic option in this setting but is rarely used. The reason for denying LT is that it requires abstinence from alcohol for six months before consideration for a transplant. This period is arbitrary and has never been shown to affect survival after LT (1). Even where there is evidence that shorter pre-listing abstinence correlates to shorter time to first drink post-transplant, an optimal period of pre-transplant abstinence remains unclear (2).

In our experience seven patients with severe AAE (Model End Stage Liver Disease over 21 and Maddrey Discriminant Function over 32) and type 1 HRS and non-responders to medical therapy, were submitted to transjugular intrahepatic portosystemic stent shunt (TIPS) and successively transplanted within five months of abstinence (median age 49 years) (unpublished data). None of the patients relapsed after a period of 5 years. Castell *et al.* (11) listed 22 patients for transplantation (median age 47 years) within 15 days of non-response to treatment and 18 patients were transplanted within 9 (range 5-13) days (2 died on the waiting list, 2 recovered). Non-responders to steroids were identified by a Lille score of 0.45 or higher, or worsening of liver function, seven days after presentation. Six-month survival was 83% (compared with 44% in a non-randomised case-matched control group). None of the patients relapsed in the first year although one patient relapsed after 917 days (1 unit/ three times week). Considering that patients who do not recover within the first 3 months of abstinence are unlikely to survive (12) in case of AAH, 3 months of alcohol abstinence may be more ideal than 6 months. Varma *et al.* (2) affirm that there is absence of enough evidence to support the 6 months sobriety. It is unclear whether this is an effective predictor for post transplant abstinence or simply a method of consistent selection popular with insurance companies. Shawcross and O'Grady (12) underlined that a teenager who develops liver failure after a deliberate paracetamol overdose, after taking ecstasy, or after contracting hepatitis B through irresponsible sexual behaviour will have open access to LT. Why should his or her peer who simply drank too much for a few months be treated differently? (12).

A strict application of a period of sobriety as a policy for transplant eligibility is unfair to non-responder patients, as most of them will have died prior to the end of the 6-month sober period (13). In our opinion, in case of severe AAH, subjects with a good social support, without psychotic or personality disorders, should be referred to LT if they still have decompensated liver disease and 3 months of abstinence.

Post-LT, patients with limited comorbidities and good social support should be offered individual cognitive behavioural therapy. Those with significant comorbidities and/or limited social support, should be offered multi-component programmes (multidimensional family therapy, functional family therapy, brief strategic family therapy) (14). The frequency of self-help groups, of which the best known is alcoholics anonymous, is mandatory. We agree with Kotlyar *et al.* (15) that the lack of pre-LT abstinence alone should not be a barrier against being listed.

Hepato-Gastroenterology 2012; 59:00-00 doi 10.5754/hge11691
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Cirrosi Epatica Alcol Correlata e Trapianto: Sopravvivenza

Europe:

84% at 1 year; 78% at 3 years; 73% at 5 years

Burra et al, Am J Transplant 2010

USA:

92% at 1 year; 86% at 3 years; 86% at 5 years

Japan:

81.3% at 1 year; 78.5% at 3 years; 75.7% at 5 years

Testino G, 2014

CIRROSI EPATICA SCOMPENSTA E TRAPIANTO

DONAZIONE DA VIVENTE

Alcoholic Liver Disease

100% at 1 year; 91% at 3 years; 91% at 5 years

Non-Alcoholic Liver Disease

90% at 1 years; 86% at 3 years; 83% at 5 years

Kawaguchi et al; Hepatol Res 2013

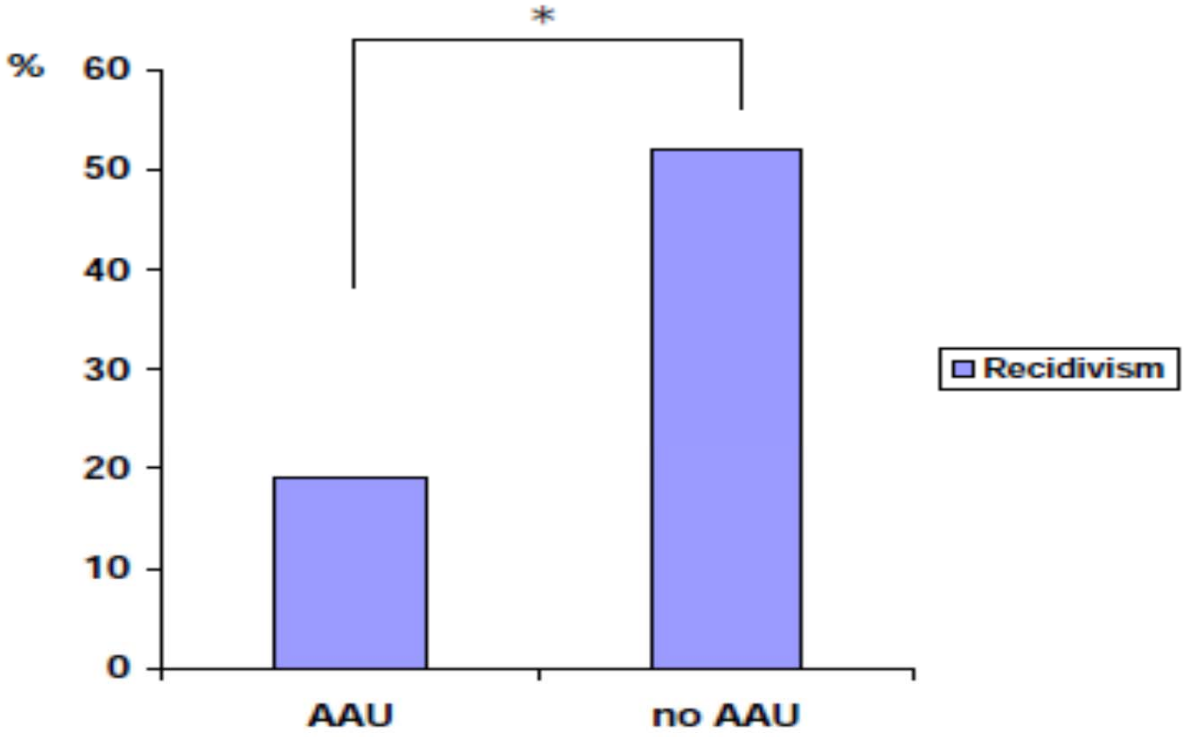


Fig. 2. Percentage of patients who showed recidivism after liver transplantation, and statistical comparison. *p = 0.005. AAU, Alcohol Addiction Unit.

Addolorato et al; Alcohol Clin Exp Res 2013

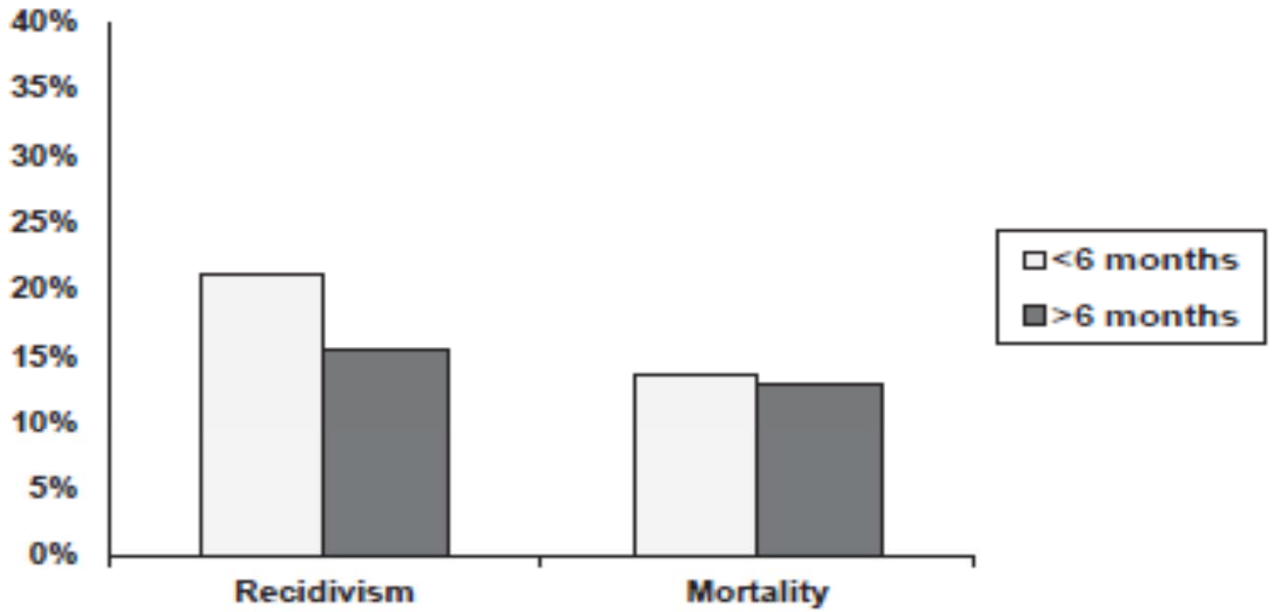


Fig. 4. Percentage of patients, followed at the Alcohol Addiction Unit (AAU), who showed recidivism, lapse, relapse, and mortality after liver transplantation, grouped on the basis of the pretransplant length of alcohol abstinence (>/<6 months; p = ns).

Addolorato et al; Alcohol Clin Exp Res 2013

Kollman et al, Transpl Int 2016

Attilia et al, Clin Transplant 2018

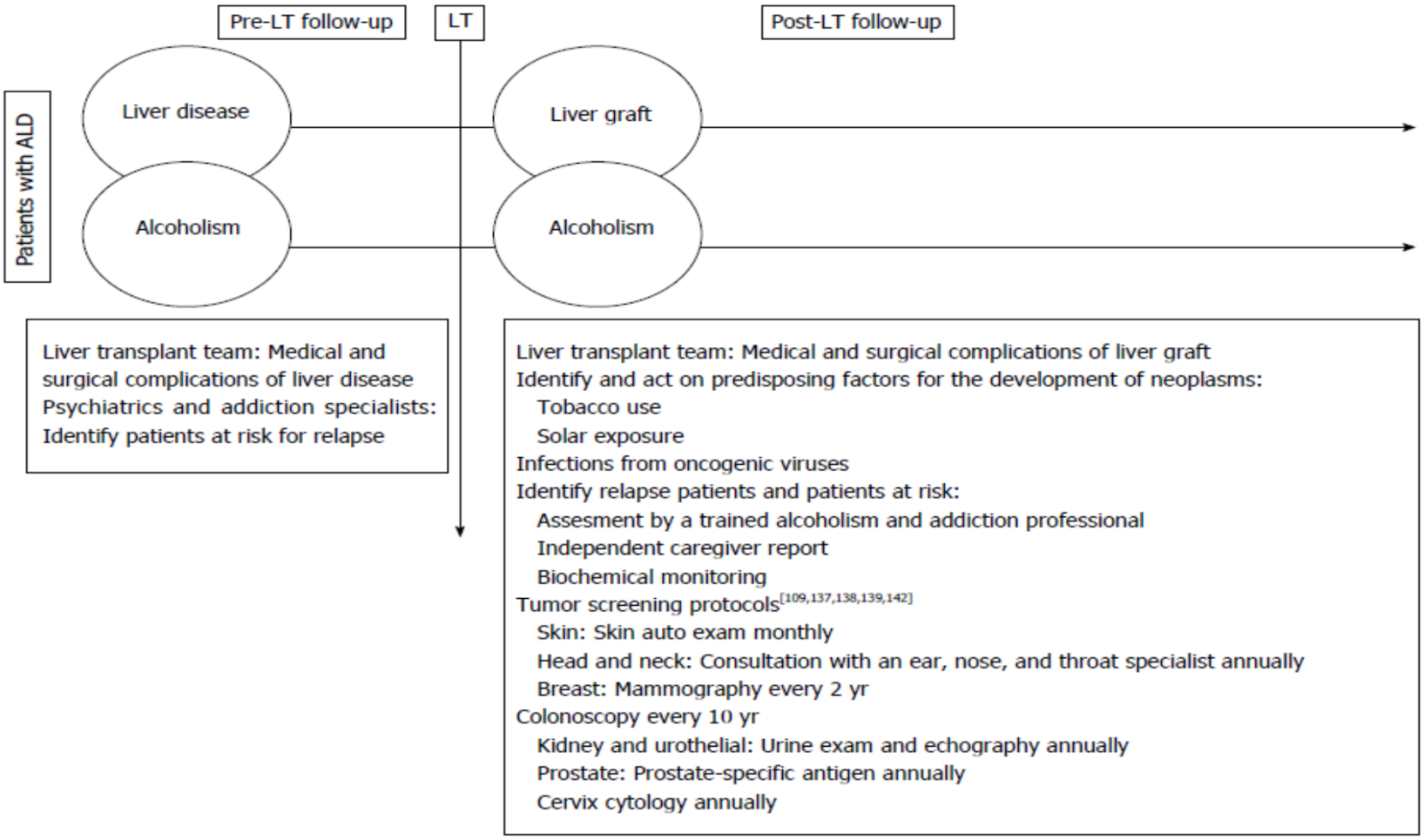


Figure 2 Proposed pre- and post-liver transplantation follow-up in alcohol liver disease. LT: Liver transplantation; ALD: Alcohol liver disease.

Iruzubieta et al; WJG 2013

ALCOHOLIC LIVER DISEASE AND LIVER TRANSPLANTATION

1) Screening of the novo tumors after LT and prevention of cardiovascular complications

2) Child-Pugh class C

3) In case of ESLD with MELD < 19 six months of abstinence are required

4) In case of progressive ESLD (first visit) with MELD > 19, three months of abstinence are more ideal than six months in selected patients

5) In case of severe AAH, not responding to medical therapy (DF > 32 or MELD > 21), LT is mandatory in selected patients independently of the sober period achieved

6) The multidisciplinary transplant team must include an Addiction Specialist/ Hepato-Alcohologist

7) <u>Patients have to partecipate to self-help groups</u>

Position Paper SIA, 2018

come completare il percorso

Trattamento Psico-Sociale: efficacia 15-40%

Edwards and Rollnick, Addiction 1997

Accoglienza/empatia/colloquio motivazionale (compliance)

Trattamento altre dipendenze (fumo soprattutto)

Trattamento Psicologico Cognitivo-Comportamentale

Terapia Strategica Breve

Auto-Mutuo-Aiuto (astensione e follow-up sobrietà)

Kelly and Yeterian, Alcohol Research Health 2011

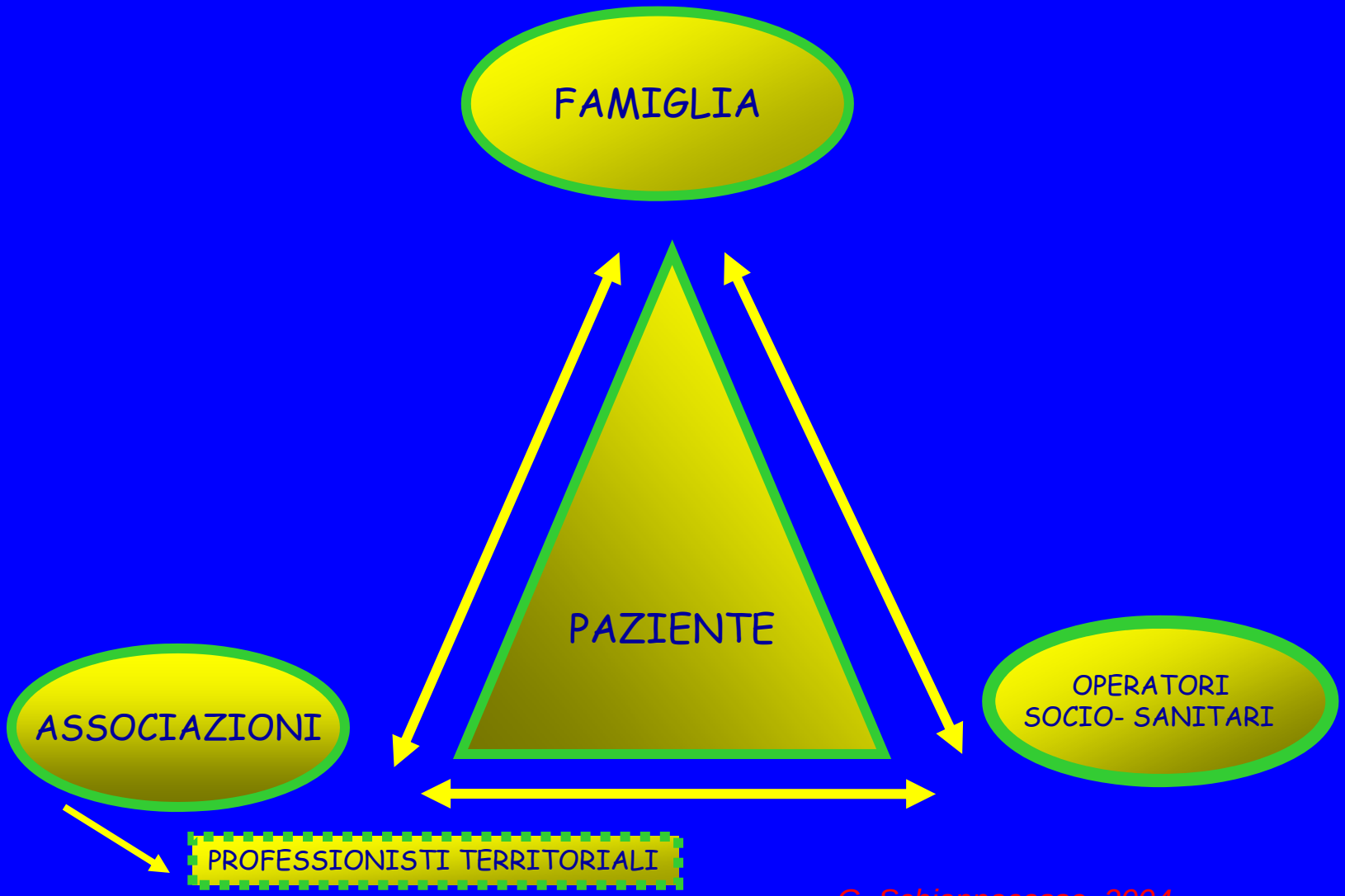
ALCOHOL USE DISORDERS (AUDs) E TRAPIANTO DI FEGATO

Position paper della Società Italiana di Alcologia (SIA)

Per lo sviluppo, il management e l'aggiornamento di linee guida e di buone pratiche cliniche per il trapianto di fegato conseguente a disturbi da uso di alcol
Integrazione Ospedale-Territorio

19) È fortemente raccomandato trattare il policonsumatore non come un monodipendente (Raccomandazione SIA: IIaC).
20) È raccomandata la collaborazione con le associazioni di auto-mutuo-aiuto (CR; Raccomandazione SIA: 1C).
21) Mandatoria una stretta sinergia fra i servizi territoriali e il team trapiantologico per la identificazione precoce e per la ottimale gestione del paziente e della sua famiglia (Raccomandazione SIA: 1C).

OBIETTIVO



G. Schiappacasse, 2004


Grazie