Forsvaret finder sted torsdag den 16.1.2003 kl. 14.00 i Auditoriet, indgang 50, Bispebjerg Hospital.

Alcohol abuse and postoperative morbidity

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LÆGEFORENINGENS FORLAG
KØBENHAVN 2002

Denne afhandling er i forbindelse med nedenstående anførte tidligere offentliggjorte artikler af Det Sundhedsvidenskabelige Fakultet ved Københavns Universitet antaget til offentligt at forsvares for den medicinske doktorgrad.

København Universitet, den 25. september 2002

Ralf Hemmingsen
Dekan

This thesis will be published as an original article in Danish Medical Bulletin.

THE PRESENT THESIS IS BASED ON THE FOLLOWING PUBLICATIONS:

1. Tønnesen H, Schütten BT, Jørgensen BB. Influence of alcohol on morbidity after colonic surgery. Diseases of the Colon and Rectum 1987; 30: 549-551.
2. Tønnesen H, Schütten BT, Tollund L, Hasselqvist P, Klintorp S. Influence of alcoholism on morbidity after transurethral prostatectomy. Scandinavian Journal of Urology and Nephrology 1988; 22: 175-177.
3. Tønnesen H, Pedersen A, Jensen MR, Møller A, Madsen JC. Ankle fractures and alcoholism. Journal of Bone and Joint Surgery (Br) 1991; 73-B: 511-513.
4. Sonne NM, Tønnesen H. The influence of alcoholism on outcome after evacuation of subdural haematoma. British Journal of Neurosurgery 1992; 6: 125-130.
5. Felding C, Jensen LM, Tønnesen H. Influence of alcohol intake on postoperative morbidity after hysterectomy. American Journal of Obstetrics and Gynecology 1992; 166: 667-670.
6. Tønnesen H, Petersen KR, Højgaard L, Stokholm KH, Nielsen HJ, Knigge U, Kehlet H. Postoperative morbidity among symptom-free alcohol misusers. Lancet 1992a; 340: 334-337.
7. Tønnesen H, Kaiser AHH, Nielsen BB, Pedersen AE. Reversibility of alcohol-induced immune depression. British Journal of Addiction 1992b; 87: 1025-1028.
8. Tønnesen H, Carstensen M, Maina P. Is carbohydrate deficient transferrin a useful marker of harmful alcohol intake among surgical patients? European Journal of Surgery 1999a; 165: 522-527.
9. Tønnesen H, Rosenberg J, Nielsen HJ, Rasmussen V, Hauge C, Pedersen IK, Kehlet H. Effect of preoperative abstinence on poor postoperative outcome in alcohol misusers: randomised controlled trial. British Medical Journal 1999b; 318: 1311-1316.

PREFACE

This thesis is based on work performed in collaboration between several departments in the Copenhagen Hospital Corporation and in Copenhagen County. The work was rooted in the Department of Surgical Gastroenterology, Hvidovre Hospital, and completed at the Clinical Unit of Preventive Medicine and Health Promotion, Bispebjerg Hospital.

I am indebted to Professor *Henrik Kehlet,* chief surgeon at the Department of Surgical Gastroenterology, for scientific guidance and for many good discussions and constructive criticism. I thank Professor *Poul Martin Christiansen* for his support in the initial phase, *Bjørn Andersen* for fruitful statistical discussions and *Finn Hardt* for clinical guidance with regard to alcohol abuse.

I am grateful to my co-workers. My special thanks to *Liselotte Højgaard, Kresten R. Petersen, Hans-Jørgen Nielsen, Jacob Rosenberg, Birgitte T. Schütten, Ann Møller, Jesper Clausager Madsen, Knud Heine Stokholm, Christine Felding, Nan Sonne, Pierre Maina,* and *Mads Carstensen*, all of whom made significant contributions to the work.

I also thank laboratory assistants *Mette Wolmer, Karin Hoborg Juhl,* and *Annie Høj,* and especially secretary *Ann-Kristin Andreassen.*

In particular, thanks to all the patients who participated in the studies and to the clinical staff.

The studies and review were supported by the Danish Medical Council, the "Danmark" Health Foundation, the Danish Ministry of Health's Funds for Alcohol Research, Pharmacia & Upjohn, and the Foundation for the Alcohol Research Center.

To my family

Hanne Tønnesen
Copenhagen, October 2002

CONTENTS

I. Alcohol and surgery

INTRODUCTION AND AIM

Alcohol abuse is a worldwide problem associated with physiological and psychosocial complications. The personal and economical consequences are tremendous. Alcohol-induced medical disorders, such as hepatic cirrhosis, pancreatitis, and polyneuropathy, are well known. However, a high consumption of alcohol also seems to be associated with a poorer outcome after surgery.

Patients who drink too much have more complications after surgery, even when abuse is asymptomatic. The most common complications seen are infections, cardiopulmonary insufficiency, bleeding episodes and withdrawal syndrome (*Tønnesen* 1992c, *Tønnesen* 1992d, *Møller & Tønnesen* 1997, *Danish Ministry of Health* 1999, *Tønnesen & Kehlet* 1999c, *Tønnesen* 1999d, *Tønnesen* 1999e, *Spies et al* 2001, *Danish National Board of Health* 2001). These complications indicate that the mechanisms involve immune capacity, cardiac function, haemostasis, and stress reaction.

The association between alcohol and surgery is important for several reasons: a high alcohol intake is common, surgical complications are always troublesome, and the problem may be preventable by early intervention.

The aim of this thesis was to evaluate

- evidence
- possible mechanisms
- prevention

of the increased postoperative morbidity in alcohol abusers.

II. Definitions of alcohol abuse

There are several definitions of alcohol abuse. The international definition is broad and includes any alcohol-related physical, psychological, or social disorder (*Morse & Flavin* 1992, *Madden* 1993). But this definition is difficult to apply in clinical daily life and the WHO considers an intake above 20 g of ethanol per day harmful.

The National Boards of Health in most countries have introduced drinking limits in their campaigns for prevention of alcohol abuse. The limits in Denmark are 14 drinks per week for women and 21 for men. One drink contains 12 g of ethanol. These limits are well implemented in the population and are useful for screening procedures in order to identify persons, who should be offered intervention.

The prognosis of treatment for alcohol problems is related to the development of dependence, characterised by the following diagnostic criteria: loss of control, inability to cut down, tolerance, craving, withdrawal symptoms, and blackouts (*American Psychiatric Association* 1987, *World Health Organisation* 1992). It is therefore relevant for alcohol treaters to distinguish between a high alcohol intake and alcohol dependence in the diagnostic procedure.

In contrast, the organ damage is primarily related to the amount consumed over time, and somatic departments routinely register the daily consumption in the medical records.

Irrespective of definition, the effect of treatment is measured by reduction in the alcohol intake and/or alcohol-free days. It is therefore important to include consumption in the alcohol case history.

DEFINITIONS USED IN THE FOLLOWING

A strict definition of alcohol abuse for surgical use is lacking. I have therefore defined abuse as a self-reported consumption of at least five drinks per day in all our studies. The control groups are defined by a consumption of no more than two drinks per day, which was the average consumption in Denmark during the study period (*Danish Statistical Yearbooks* 1985-1998). Alcohol abusers are those without clinical symptoms of consumption, particularly no liver cirrhosis or hepatitis, unless stated otherwise.

III. Postoperative morbidity in asymptomatic alcohol abusers

THE ASSOCIATION

The literature was reviewed for evidence of increased postoperative morbidity in asymptomatic alcohol abusers. The strategy comprised a broad search in the databases Medline/Pubmed, Embase, and Cochrane Library, and references from identified papers supplemented by repeating manual searches. Only original studies of alcohol abuse/alcoholism and surgery/operation in humans and published in English, French, German, Swedish, Norwegian, or Danish were reviewed. Further criteria were that the patients had undergone an operation, the alcohol history/relevant categories were described, and the postoperative outcome had been measured and evaluated in relation to alcohol.

Excluded were articles concerning children and patients suffering from hepatic cirrhosis, hepatitis, pancreatitis, Korsakoff-Wernicke syndrome, or other alcohol-induced chronic diseases; in addition, the following studies with no relevant criteria for inclusion or outcome measures, such as

A. relevant surgical intervention (for instance, puncture, endoscopy, tubulation, or inclusion of patients not undergoing operation) (*Karlstrom & Olerud* 1974, *Ovadia et al* 1986, *Destandau et al* 1987, *Brezel et al* 1988, *Passeri et al* 1993, *Ring & Sattler* 1994, *Thonke et al* 1994, *Nyquist et al* 1997, *Gerke et al* 1998, *Sheehan et al* 1999, *Mathog et al* 2000)
B. relevant alcohol history (for instance, no categorisation of alcohol abuse or an alcohol history obtained without relation to the operative period) (*Conron & Hardy* 1976, *Höckerstedt et al* 1982, *Parrot & Grosset* 1988, *Rogers et al* 1989, *Williams-Russo et al* 1992, *Berge & Gilhuus-Moe* 1993, *Eubanks et al* 1993, *Beckhardt et al* 1994, *Berge & Bøe* 1994, *Klein et al* 1996, *Espehaug et al* 1997, *Romano et al* 1997, *Woolson & Rahimtoola* 1999, *Karl et al* 2000)
C. sizeable study populations (for instance, inclusion of very few alcohol abusers or development of very few complications (*Bjerkelund et al* 1986, *Friedman & Cochran* 1987, *Del Rizzo et al* 1994, *Macnamara et al* 1994, *Mäkelä et al* 1995, *Nölle et al* 2000)
D. evaluation of the postoperative outcome in relation to alcohol history (*Sullivan & Waddell* 1968, *Aukee* 1973, *Rittenhouse et al* 1976, *Dean et al* 1977, *Bambach et al* 1978, *Hungerford & Zizic* 1978, *Takaku et al* 1979, *Shead & Shah* 1980, *Coupal et al* 1981, *Lennard et al* 1985, *Alden et al* 1989, *Katlic et al* 1990, *Nguyen et al* 1990, *Iizuka & Lindqvist* 1992, *Tørgersen & Tornes* 1992, *Martella & Santos* 1995, *Merlicco et al* 1995, *Weed et al* 1995, *Yokoyama et al* 1995, *Oliver et al* 1996, *Perelman & Strelzov* 1997, *Canver et al* 1998, *Lynch et al* 1998, *Stark & Nathanson* 1998, *Chan et al* 2000)
E. very long-term outcome or non-specific description of the outcome (*Katzner et al* 1978, *Knop & Fischer* 1981, *Boulay et al* 1983, *Moran et al* 1983, *Fischer et al* 1985, *Dorr et al* 1986, *Krähe & Zielke* 1986, *Norotte et al* 1988, *Nagasue et al* 1989, *Okada et al* 1995, *Ritter et al* 1997, *Fink & Rüther* 2000, *Minami et al* 2000, *Schryvers et al* 2000)

Thirty-one papers were left for further analyses, seven of which were articles by the author and co-workers. The estimated evidence (*Pedersen et al* 2001) and the calculated odds ratio are given in Table A in the appendix and Fig. 1, respectively.

On the definition given above, alcohol abusers who drink at least 60 g of ethanol per day have an increased postoperative morbidity, OR ranging from 3.1–26.6, being 6.7 in median value (Table A in the appendix). Overall, they stayed 1.7 times longer in hospital (OR from 1.0–6.0), probably because of the increased development of complications after surgery, which may also explain these patients' need for more nursing (*Tønnesen et al* 1992a, *Tønnesen et al* 1999b). They tended to require more second surgery, OR = 3.8 (2.1-5.1), and the long-term outcome also seemed poorer (*Tønnesen et al* 1988, *Tønnesen et al* 1991, *Sonne & Tønnesen* 1992, *Klausen et al* 2000). Postoperative mortality was increased, OR = 3.0 (1.0–24.5), but only reached significance in three studies *(Sonne & Tønnesen* 1992, *Spies et al* 1996, *Neuenschwander et al* 2002) (Table A in the appendix).

ALCOHOL HISTORY

Seven to twenty per cent of patients admitted to surgical departments reported a consumption of at least five drinks per day, with men being overrepresented (*Chick et al* 1985, *Nielsen et al* 1994, *Rambaldi et al* 1995, *Tønnesen et al* 1999a). The prevalence was 7% to 49% in patients undergoing elective surgery (*Tønnesen et al* 1987, *Tønnesen et al* 1988, *Felding et al* 1992, *Tønnesen et al* 1992a, *Stopinski et al* 1993, *Spies et al* 1995a, *Spies et al* 1996) and 14% to 38% in trauma patients requiring emergency intervention (*Antti-Poika et al* 1988, *Tønnesen et al* 1991, *Sonne & Tønnesen* 1992, *Høidrup et al* 1999).

The wide range in prevalence probably reflects inclusion of alcohol-related diagnoses in some of the studies (*Sonne & Tønnesen* 1992, *Spies et al* 1995a, *Spies et al* 1996). Furthermore, the number of abusers may vary from one area to another, depending on the definition, as well as consumption, alcohol-related disorders, age, and gender distribution in the population.

Most surgical authors define abuse by self-reported intake, which is open to variation in the memory of the patients (*Fonager & Sabroe* 2001). Though the validity

seems high (*Grønbæk & Heitmann* 1996), underestimation is more pronounced with a high intake (*Orrego et al* 1979, *Popham & Schmidt* 1981). Some patients in the control groups may, therefore, in fact, belong to the group of abusers, whereas the reverse seems improbable. As the studies have shown remarkable differences in the morbidity of abusers and controls, the possibility of unreliable self-reports on alcohol intake should not change the conclusion.

A more precise identification of consumption by other methods could reveal a dose-dependence between alcohol intake and postoperative morbidity, which has been overlooked hitherto. This hypothesis would be supported by an improvement in the postoperative outcome following a preoperative reduction in alcohol consumption, without complete abstinence. These issues are discussed in other chapters.

BIAS AND LIMITATIONS

Bias and limitations should be considered in relation to the literature evaluated, including our own studies. Except for one publication (*Tønnesen at al* 1999b), this literature consisted of observational studies based on a wide range of designs, alcohol categories, surgical procedures, and outcome measurements (Table A in the appendix). Our randomised study is the only one at present. The lack of

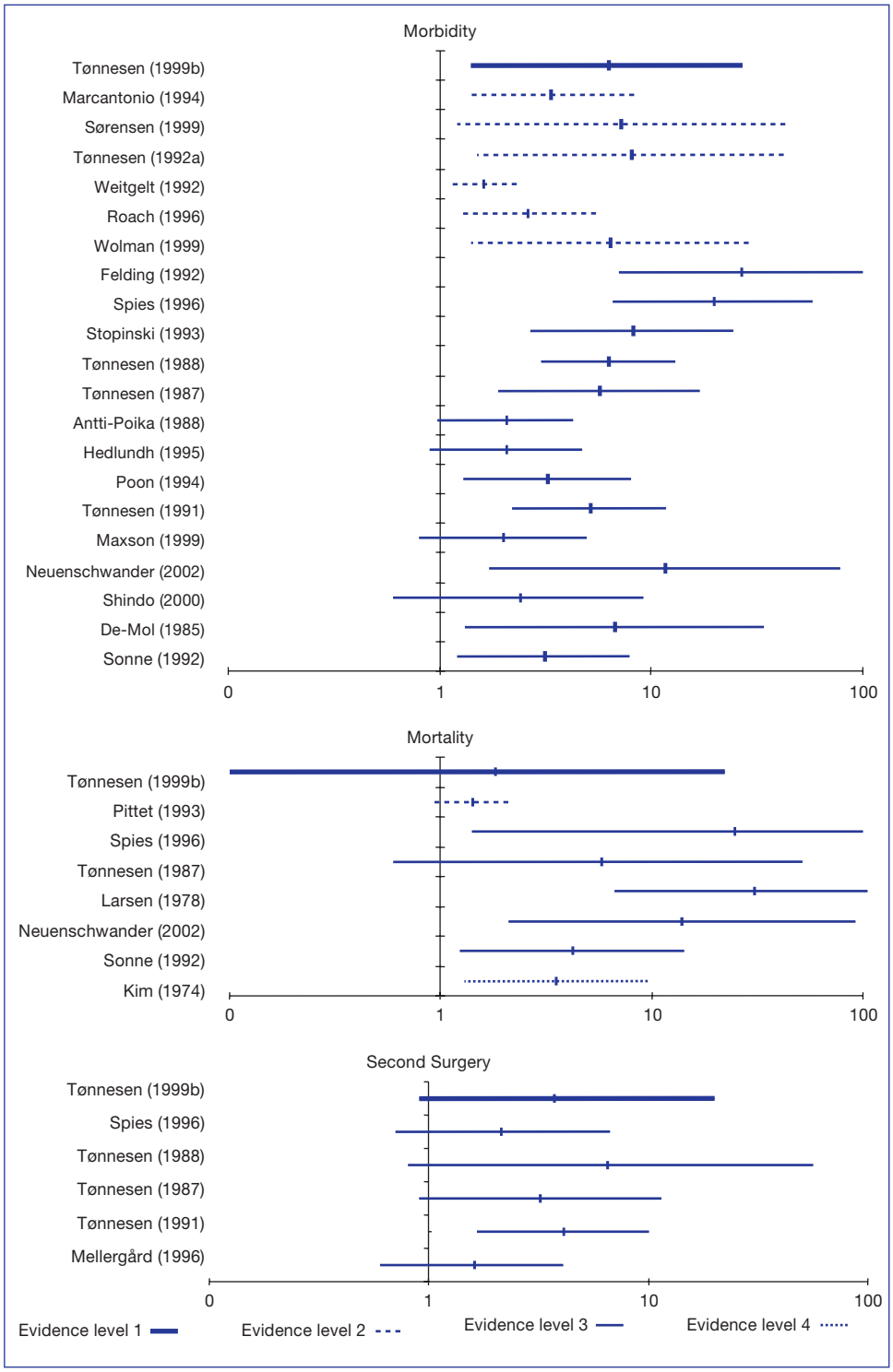

Fig. 1. *Association between alcohol and postoperative outcome: OR (95% ci) (References are given in Table A in the appendix).*

publications could be caused by problems in overcoming the great difficulties of performing randomised clinical studies that interfere with life-style. A meta-analysis was therefore not performable.

Definition of alcohol abuse, criteria for complications, registration of second surgery, or adjustment for confounders were often lacking.

None of the studies were blind, thereby adding to the risk of biased observation and registration. However, attempts were made to perform some of the procedures and analyses in an observer-blind set-up (*Tønnesen et al* 1987, *Tønnesen et al* 1988, *Tønnesen et al* 1991, *Felding et al* 1992, *Sonne & Tønnesen* 1992, *Tønnesen et al* 1992a, *Tønnesen et al* 1999b). Most of the studies were retrospective with surgical cohorts or as case-control studies based on surgical cohorts.

The alcohol history was improved in the prospective investigations by using a structured interview (*Felding et al* 1992, *Tønnesen et al* 1992a, *Stopinski et al* 1993, *Spies et al* 1996, *Tønnesen et al* 1999b), supplemented by a specific test and/or diagnostic criteria for addiction (*Tønnesen et al* 1992a, *Spies et al* 1996). The alcohol history was never validated by collateral case histories or biological markers. Duration of alcohol abuse was partly included in only one study (*Tønnesen et al* 1992b). The prospective design also increased the possibility of better methods and registration, as well as interventional procedures, scheduled follow-ups, and measurement of intermediate data for pathophysiological evaluation. A poor alcohol history may mix heavy long-term abusers with milder abusers in the alcohol group and/or overlook abusers in the control group, thereby diluting an association between alcohol abuse and postoperative outcome.

In several of the publications the study population, number of alcohol abusers entered, the frequency of complications, deaths, and/ or second surgery were small, thereby reducing the possibility of confirming or disproving significance. On the other hand, some of the sizeable studies were restricted to a single type of complication, and did not make the best possible use of the large study population (*Marcantonio et al* 1994, *Roach et al* 1996, *Wolman et al* 1999).

The statistical procedures were simple in most of the studies, chi^2 test or Fisher's exact test, without adjustment for confounders related to the patient, the disease, the treatment, or the organisation, all of which influence the outcome (Table A in the appendix). The matched case-control design was intended to control for surgical risk factors other than alcohol in some studies (*Tønnesen et al* 1987, *Tønnesen et al* 1988, *Tønnesen et al* 1991, *Tønnesen et al* 1992a), but not all (*Hedlundh & Fredin* 1995). The logistic regression analysis included the possibility of adjustment for confounders that influence the outcome after surgery (*Pelczar et al* 1993, *Roach et al* 1996, *Sørensen et al* 1999, *Wolman et al* 1999).

A poorer outcome, especially in alcohol abusers, may be because additional risk factors are more pronounced during drinking, for instance smoking, dysnutrition, severe liver disease, which have not been monitored. Unfortunately, few studies excluded involvement of liver disease by hepatic biopsies (*Tønnesen et al* 1992a, *Tønnesen et al* 1999b), anamnestic or clinical signs (*Tønnesen et al* 1987, *Tønnesen et al* 1988, *Tønnesen et al* 1991, *Sonne & Tønnesen* 1992), or registered nutritional status (*Tønnesen et al* 1992a, *Rantala et al* 1997, *Tønnesen et al* 1999b) and smoking habits (*Tønnesen et al* 1987, *Tønnesen et al* 1988, *Tønnesen et al* 1991, *Felding et al* 1992, *Sonne & Tønnesen* 1992, *Tønnesen et al* 1992a, *Sørensen et al* 1999, *Tønnesen et al* 1999b). These risk factors may also be reduced when alcohol is withdrawn, thus contributing to the improved postoperative outcome after preoperative cessation of alcohol intake (*Tønnesen et al* 1999b) and thereby overestimating the influence of alcohol abuse on postoperative morbidity.

The results seem to become more significant with improvement in the methodology, which permits evidence to be gathered on a positive association between alcohol abuse and increased postoperative morbidity.

None of the papers described a protective effect of alcohol abuse on postoperative complications, which does not exclude negative findings when publication bias of significant results is taken into account.

Although the early studies of the author and co-workers could be criticised as mentioned above, they supplement the weak to moderate evidence published by others and our latest paper (*Tønnesen et al* 1999b) seems to provide new evidence on the issue.

COSTS

The total costs of alcohol abuse have been estimated in more and more details over the years. The latest reports are from Canada (*Single et al* 1996) and Denmark (*Danish Ministry of Health* 1999), two countries with comparable health service systems. The total costs in direct health care are estimated to be US$ 46 and US$ 64 per capita of the total population, respectively. The major difference lies in the inclusion of postoperative morbidity in alcohol abusers in the Danish report.

CONCLUSION

The literature could be criticised for several methodological flaws. Nevertheless, the results were in agreement showing moderate to strong evidence of increased postoperative morbidity after surgical procedures on alcohol abusers who reported drinking at least five drinks per day. There is weak to moderate evidence of increased postoperative mortality, hospital stay, and re-operation. The personal and economic consequences are tremendous. The incidence of alcohol abusers undergoing surgery was 7% to 49%, according to gender and diagnosis. They have been identified by a self-reported alcohol intake, which implies the possibility of underestimation.

IV. Alcohol markers

Alcohol markers could be used for a more precise identification of alcohol abuse and subsequently reveal new associations between alcohol and surgery.

An ideal alcohol marker for surgical patients should be reliable, handy, inexpensive, and related to postoperative outcome. Short-term abuse and preoperative abstinence from alcohol should be recognised in the test result, but other preoperative conditions such as dehydration, blood transfusion, or the disease itself should not affect the outcome. High predictability of the alcohol markers is especially necessary for surgical patients, because the clinical consequences of continuous alcohol abuse are immediate and tremendous.

ALCOHOL QUESTIONNAIRES

Prospective studies offer the possibility of a structured interview on consumption. This can be supplemented by indirect markers of abuse (*Tønnesen et al* 1992a, *Spies et al* 1996), such as the Michigan alcoholism screening test, MAST (*Selzer* 1971), CAGE, which is an acronym for: cut down, annoyed, guilty, eye opener (*Ewing* 1984), the alcohol use disorders identification test, AUDIT (*Saunders et al* 1993a, *Saunders et al* 1993b), and the criteria according to the diagnostic and statistical manual of mental disorders, DSM (*American Psychiatric Association* 1987) or to the international classification of diseases, ICD (*World Health Organisation* 1992). The aim of these questionnaires and diagnostic criteria is to identify symptoms of dependence and other alcohol-related problems necessitating intervention. The questionnaires are inexpensive, easy to use, and independent of the disease requiring surgery.

However, short-term abuse and periods of abstinence for less than six to 12 months in the DSM and AUDIT or longer in the other tests are not detectable. Furthermore, abuse without concomitant dependence would be overlooked, because most of the questions are related to symptoms of dependence (Table I).

BIOLOGICAL MARKERS

The biological markers most often used are carbohydrate deficient transferrin, CDT, gamma-glytamyl transferase, GGT, mean cell volume of erythrocytes, MCV, and blood alcohol concentration, BAC (Table II). They are more directly related to alcohol consumption than are the questionnaires, which, hypothetically, make them more useful in identifying alcohol abuse in surgical patients. However, they require laboratory back-up, which delays the diagnosis. The results are not independent of preoperative conditions, such as hydration and blood transfusion. The half-life of MCV is too long for detection of four weeks of preoperative abstinence. The half-life of BAC is too short for identification of an intake of five to ten drinks per day if distributed all over the daytime.

CDT seems the most attractive test because it becomes positive at the harmful consumption of at least five drinks per day for at least two weeks (*Stibler* 1991) and because the half-life should permit recognition of one month of (preoperative) abstinence. However, wide ranges in validity (Fig. 2) and correlation coefficients, 0.20–0.77, have been reported. This may, in part, be due to differences in analytical methods, cut-off values, and characteristics of the study populations, such as alcohol consumption, hydration, and time since the last drink (Table B in the appendix).

Table I. *Alcohol dependence. Comparison of criteria and questions in commonly used diagnostic tools (references in the text).*

Questions concerning:	DSM-III-R	ICD-10	CAGE	MAST	AUDIT
Last symptom	III-R: 6 months IV: 12 months	(not given)	ever	ever	last year
Inability to cut down/stop drinking	+	+	+	+	+
Giving up important activities/annoyance	+	+	+	+	+
Guilty/continuous drinking, despite negative consequences	+	+	+	+	+
Withdrawal symptoms/eye-opener	+	+	+	+	+
Tolerance	+	+	–	–	–
Craving	–	+	–	–	–
Blackout symptoms	–	–	–	+	+
Requiring treatment	–	–	–	+	–
Amount of alcohol	–	–	–	–	+

Table II. *Characteristics of commonly used biological alcohol markers.*

	CDT	GGT	MCV	BAC
Half-life	2 weeks	4 weeks**	2-3 months	hours
Influenced by:				
Liver disease	+*	+	+	+
Dehydration/rehydration	+	+	+	+
Blood transfusion	+	+	+	+
Intake required for a positive test result	≥ 5 drinks per day for 2 weeks	unknown	unknown	> 1 drink per hour

*) % CDT is not influenced, because it gives CDT in per cent of transferrin.
**) Alcohol abusers without liver disease.

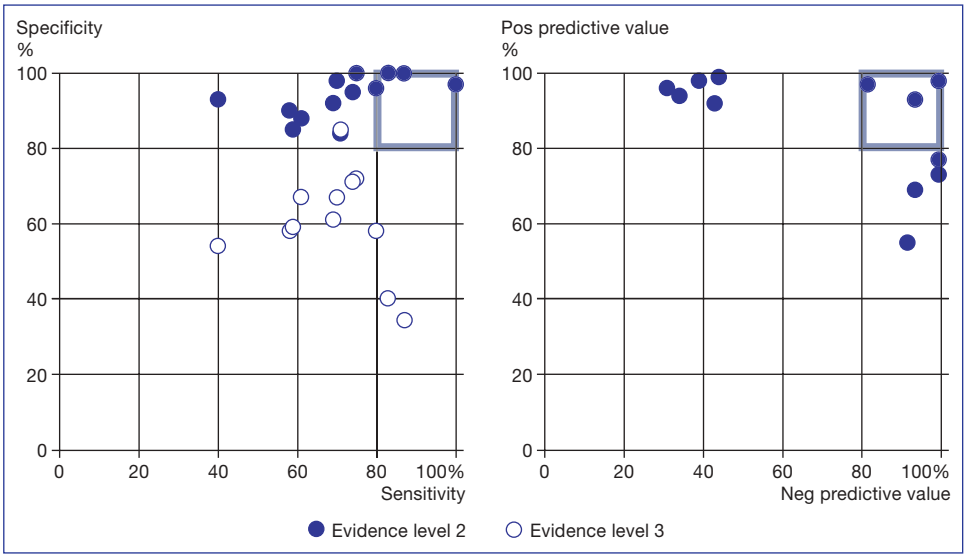

Fig. 2. *Studies of CDT in somatic hospital patients. The optimal position is in the upper right quadrate. Left: Sensitivity related to specificity. Right: Negative predictive value related to positive value (References are given in Table B in the appendix).*

A small study we carried out showed a fair correlation coefficient, r = 0.58 in 286 women and r = 0.77 in 248 men. The validity was relatively high in 80-100%, except for a low positive predictive value of 44% in women (*Tønnesen et al* 1999a). However, the study had several flaws, such as reporting of a weekly instead of a daily consumption.

Although CDT seems the most attractive of the alcohol markers, systematic reviews, including a meta-analysis, did not find it a significantly better marker of alcohol abuse than GGT (*Salaspuro* 1999, *Scouller et al* 2000). The performance of both markers was better in hospital settings than in primary health care settings or population studies (*Salaspuro* 1999).

ALCOHOL MARKERS AND POST OPERATIVE OUTCOME

Biological markers and questionnaires have not been evaluated as main predictors of the postoperative outcome, except in one recent study (*Maxson et al* 1999).

In this study, CAGE-positive and CAGE-negative patients did not differ in developing postoperative organ failure and withdrawal syndrome, seven of 31 patients and 37 of 290, respectively. Alcohol withdrawal syndrome was recognised in both groups after surgery.

This study did not include the volume of alcohol intake or the validity of the CAGE scoring. The inclusion criterion was postoperative stay in the intensive care unit. Patients who did not require intensive care after surgery were excluded and the most common complication in alcohol abusers, wound complication, was not evaluated. The study design was therefore not optimal for investigating an association between alcohol and postoperative outcome.

Biological markers may be attractive in unconscious patients in clinical daily life, but they have not been evaluated in that kind of set-up.

Until there is enough evidence as to the preferred alcohol markers, a structured interview about the current alcohol intake, preceded by information to the patient about the increased risk during surgery, is preferable as a routine procedure in surgical patients.

CONCLUSION

Biological markers such as CDT, GGT, MCV, and BAC or questionnaires like CAGE, MAST, and AUDIT raise new interpretation problems. The inability of the questionnaires to detect short-term intake and abstinence or abusers without dependence, the inconsistent predictive values of the biological markers, and the lack of evidence of an association to postoperative morbidity in both the markers and questionnaires reduce their usefulness for identification of alcohol patients at risk during surgery.

A detailed alcohol history is therefore recommended.

V. Pathophysiology in alcohol-induced organ failure prior to surgery

Alcohol abusers develop more postoperative infections, cardiopulmonary insufficiency, and bleeding episodes than do control patients. The mechanisms of the increased postoperative morbidity involve preoperative alcohol-induced cardiac, immune, haemostatic, and endocrine dysfunction in combination with intra-operative alterations. Alcohol-induced organ dysfunction has been investigated in non-surgical patients. This literature consists of open observational studies, which include controlled investigations of alcoholic patients before and after withdrawal and of volunteers before and after alcohol intake. Parts of the procedures and analyses have been performed in an observer-blind set-up. The literature should be interpreted with caution, as mentioned above under "bias and limitations" in chapter III.

CARDIAC DYSFUNCTION

Alcoholic cardiomyopathy is characterised by a dilated left ventricle and reduced ejection fraction with no other evident aetiology in patients with a history of alcohol consumption above 80 g of ethanol per day for more than 10 years (*Richardson et al* 1986). The threshold dose for the development of cardiomyopathy is probably lower in women (*Urbano-Marquez et al* 1995). Discrete changes are preclinical myocardial damage and arrhythmias in the absence of clinical symptoms. The incidence of asymptomatic changes differs from 12% to 33% in alcohol abusers, depending on the study population. In a large Spanish investigation of 150 abusers, one-third of the men and women had evidence of subclinical cardiomyopathy with a low ejection fraction (*Urbano-Marquez et al* 1995). In three small studies, three of 15, three of 25, and three of 12 abusers without pre-existing heart disease showed signs of myocardial damage (*Kelbæk et al* 1987, *Cerqueira et al* 1991, *Ballester et al* 1997). These results are comparable to our finding that alcohol abusers scheduled for colorectal surgery had a significantly lower left ventricular ejection fraction than had matched controls, 54% (44-67) vs 68% (55-75), before surgery (*Tønnesen et al* 1992a).

The threshold value for development of cardiac myopathy, 80 g of alcohol per day, is somewhat higher than the inclusion criterion of 60 g per day in our study (*Tønnesen et al* 1992a), in which the alcohol group had been drinking 72 g per day (range 60-180) for 27 years (7-51), for instance more than half the alcohol group had a consumption below the threshold value, but over a longer period. The prolonged drinking period may add to the risk of a reduced ejection fraction, which is seen in half our alcohol group.

The precise mechanism by which alcoholic cardiomyopathy develops is still unknown, but a direct myotoxic effect of alcohol on the cellular ultrastructure is implicated. This was described 30 years ago (*Alexander* 1967) and later confirmed in a dose-dependent manner (*Urbano-Marquez et al* 1989, *Sudarikova et al* 1997). The myocardium is characterised by swollen mitochondria and a distended and cystic sarcoplasmic reticulum, which are probably related to the blockade of cardiac protein synthesis (*Tiern et al* 1985). The result may be the degeneration of myocardial fibres, also described. The myopathic changes are ubiquitous in most striated muscles, skeletal, as well as cardiac (*Urbano-Marquez et al* 1989).

The reduced systolic function is perhaps preceded by impairment of diastolic function, which was present in about one-third of 77 alcohol abusers without cardiomyopathy (*Fernandez-Sola et al* 2000). Another direct effect concerns the cardiac electromechanical coupling. Blockade of the calcium-myofilament interaction has been shown in vitro (*Gubby & Littleton* 1995), and ethanol may induce pronounced alteration of the adrenergic signal transduction system of the myocardium in vivo, thus resulting in dyscontractility (*Strasser et al* 1996), which precedes the hypertrophy (*Piano & Schwertz* 1997).

Biopsies show that about one-third of alcohol abusers compared to one-tenth of non-abusers suffering from clinical cardiomyopathy have discrete myocarditis with lymphocyte infiltration in association with myocyte degeneration or focal necrosis, and antibodies against cardiac protein acetaldehyde adducts, which suggests immunopathogenetic involvement (*Vasiljevic et al* 1990, *Olsen* 1991, *Harcombe et al* 1995).

IMMUNOSUPPRESSION

The potential clinical relevance of immunosuppression includes increased acquirement of infections and cancer in non-surgical alcohol abusers (*Tønnesen et al* 1994, *Saitz et al* 1997, *Tønnesen et al* 1999f). Other functional effects are bacterial overgrowth in the upper gastrointestinal tract (*Hauge et al* 1997), bacteriuria (Table C in the appendix), weaker immunisation after vaccination (*Rosman et al* 1997), and reduced delayed-type hypersensitivity, DTH (*Tønnesen et al* 1992b). The latter impairment is of particular surgical relevance, because reduced DTH is associated with an increased risk of infectious complications after surgery (*Christou* 1985, *Moesgaard & Lykkegaard-Nielsen* 1989). However, exclusion of alcohol abusers or adjustment for alcohol intake has not been performed in surgical DTH studies.

The threshold at which ethanol induces clinical symptoms of immune incompetence is unknown. All the published papers describe some degree of suppression. Human studies indicate that even a minor intake, below the limits recommended by the National Board of Health, may influence parts of the immune system relevant for the host defence against bacteria (*Szabo* 1993, *Bounds et al* 1994,

Szabo et al 1996, *Osterwald-Lenum et al* 1998). Lymphopenia seems to require at least three months of heavy drinking, which suggests that the duration of consumption is also of importance for the development of immunological damage (*Tønnesen et al* 1990).

Immune incompetence is a result of several interactions between ethanol and T cell-dependent processes. Thus, the activation (*Stefanini et al* 1996), adhesion (*Cook et al* 1994, *Cook et al* 1995), and proliferative response (*Stacey* 1984, *Mutchnick & Lee* 1988) are blocked. The number of circulating lymphocytes is reduced (*Björkholm* 1980, *Tønnesen et al* 1990, *Cook et al* 1991, *Tønnesen et al* 1992a, *Tønnesen et al* 1992b, *Sacanella et al* 1998), especially the B cells (*Cook et al* 1991, *Mili et al* 1992), probably because of a direct toxic effect on the stem cells in the bone marrow (*Sullivan & Herbert* 1964). Alteration of the lymphocyte subsets has been found in some studies, which describe an increase in $CD8^+$ (T suppressor cells and cytotoxic T lymphocytes) and/or a reduction in $CD4^+$ (T helper cells, B lymphocytes, and plasma cells) with a resulting reduction in the $CD4^+/CD8^+$ ratio, which may cause a functional anergy (*Cook et al* 1991, *Kronfol et al* 1993, *Cook et al* 1994, *Cook et al* 1996, *Laso et al* 1996, *Sacanella et al* 1998). Conversely, other authors did not observe these differences (*Watson et al* 1985, *Deviere et al* 1988, *Ishimaru & Matsuda* 1990).

These contradictory results may partly be explained by differences in study populations, such as inclusion of patients with liver disease (*Ishimaru & Matsuda* 1990), and suboptimal methodology without checking for liver disease or malnutrition (*Watson et al* 1985, *Deviere et al* 1988, *Cook et al* 1991, *Mili et al* 1992, *Kronfol et al* 1993, *Cook et al* 1994).

The mobilisation and phagocytic ability of monocytes, macrophages, and neutrophils are also blocked (*Brayton et al* 1970, *MacGregor et al* 1978, *Liu* 1979, *Mørland et al* 1988, *Mufti et al* 1988), as is the production of free oxygen radicals (*Nilsson et al* 1992), which may increase the oxidative stress resulting in the DNA damage measured in lymphocytes recently (*Mutlu-Turkoglu et al* 2000).

Reduction in natural killer cells seems to be more related to liver involvement than to active alcohol consumption (*Laso et al* 1997). Splenic hypofunction has recently been reported in alcoholic patients without liver disease, thus adding to the susceptibility to infections (*Corazza et al* 1997). A possible mechanism is stress-induced hypercorticism following ethanol administration (*Collier et al* 1998).

The consequence of immune incompetence is decreased clearance after experimental instillation of bacteria, followed by an increased risk of development of sepsis and death (*Lang et al* 1993, *D'Souza et al* 1996).

The mechanisms underlying these effects have not been fully elucidated. Some studies suggest that the alterations described above could be secondary to changes in the cytokine production and secretion in the early phase of the immune reaction. Interleukins 1 and 2, tumour necrosis factor, and interferon are especially reduced (*Jerrells et al* 1989, *Bermudez et al* 1991, *Khoruts et al* 1991, *Windle et al* 1993, *Omidvari et al* 1998, *Zhang et al* 1998). Conversely, the alcohol-induced impaired host defence to sepsis may be prevented by experimental administration of cytokine (*Lang et al* 1993); human studies have still to be performed. The number of interleukin-2 receptors is increased in alcohol abusers, which suggests that some basic stimulation still takes place (*Kronfol et al* 1993).

Early theories postulated that ethanol acts on the membrane lipids, changing their fluidity and disordering the shape and function (*Goldstein* 1984). However, the ethanol-induced alteration in fluidity is small and comparable to the change produced by a one-degree elevation in body temperature (*Franks & Lieb* 1982).

Recent data provide evidence of a direct effect of ethanol on membrane proteins that might carry binding sites for alcohol without metabolising it (*Slater et al* 1993, *Li et al* 1994). Alcohol in physiological concentrations has been shown to inhibit cell-to-cell adhesion by a direct interaction with a hydrophobic site of the extracellular proportion of an adhesion molecule of the immunoglobulin superfamily, ICAM, L1. This interaction with signalling proteins is dose-dependent and reversible (Ramanathan et al 1996). Although increasing numbers of alcohol-protein interactions have been identified (*Avdulov et al* 1996), some adhesion molecules like N-CAM in neural cells are not sensitive to ethanol (*Ramanathan et al* 1996) and several parts of the immune system, including the T cell independent antibody production and the B cell proliferative response, seem to be unaffected by drinking.

Other factors, like malnutrition, smoking, and advancing age, may also contribute to the compromised immunity in alcohol abusers, but this issue has not been adequately addressed.

HAEMOSTASIS

Alcohol consumption is associated with an increased risk of cerebral haemorrhage and with reduced morbidity and mortality from coronary heart disease and ischaemic stroke (*Constant* 1997). Prolonged bleeding time has been reported in relation to idiopathic epistaxis and surgery (*Tønnesen et al* 1992a, *McGarry et al* 1995). The effect of one drink per day has been evaluated in a small Israeli study of 28 patients suffering from coronary artery disease; decreased thrombogenic activity was reported (*McConnell et al* 1997). However, intervention studies of morbidity and mortality related to changes in haemostatic function remain to be established. The alcohol-induced effect on haemostasis occurs immediately after ingestion of one to two drinks and it lasts for several hours or days (*Renaud & Ruf* 1996). A daily consumption of 30-50 g of ethanol for four to five weeks significantly reduces coagulation by inhibiting platelet aggregation to most agonists, thrombin, ADP, adrenalin, and collagen in a dose-dependent manner (*Pikaar et al* 1987, *Pace-Asciak et al* 1996, *Pellegrini et al* 1996). Chronic alcohol abuse reduces the release of thromboxane A_2 and B_2 (*Mikhailidis et al* 1986, *Neiman et al* 1988). Through direct toxicity in bone marrow, the number

of circulating thrombocytes is reduced in these patients (*Levine et al* 1986).

Simultaneously with the coagulating defects, alcohol activates fibrinolysis (*Aikens et al* 1998), followed by elimination of plasminogen activator, which specifically binds to plasminogen activator inhibitor. The level of fibrinogen tissue plasminogen activator, and plasminogen activator inhibitor is reduced after alcohol ingestion (*Pikaar et al* 1987, *Hendriks et al* 1994, *Pellegrini et al* 1996). Experimental studies indicate that the increased plasminogen activator-mediated fibrinolytic activity is localised on the surface of the endothelial cells (*Aikens et al* 1997, *Aikens et al* 1998).

The exact interaction between alcohol and thrombocyte function remains to be established. The mechanism may involve the primary metabolite, acetaldehyde, which exerts a strong inhibitory action on platelet aggregation (*Spertini et al* 1992).

ENDOCRINE STRESS REACTION

Ethanol interacts in a complex way with the hypothalamic-pituitary-adrenocortical (HPA) axis and the sympathetic-adrenomedullary (SA) system. Experimental and human studies describe a dose-dependent two-to threefold increase in plasma ACTH, β-endorphin, adrenalin, noradrenalin, and cortisol after ingestion of ethanol. Except for the latter two, the responses are short-lived (*Thiagarajan et al* 1989, *Ogilvie et al* 1997, *Rivier* 1997).

During prolonged abuse, the HPA axis remains activated and a pseudo-Cushing syndrome may follow (*Veldman & Meinders* 1996), although adaptation often takes place resulting in a new balance between inhibitory and excitatory transmission as the outcome. The increased concentration of noradrenalin and cortisol in plasma may be due to positive reinforcement of corticotropin-releasing factor and ACTH secretion, reduced re-uptake and metabolism, and hypertrophy of the adrenal cortex (*Nevo & Hamon* 1995, *Veldman & Meinders* 1996). In contrast, other parts of the endocrine response seem to be blocked, especially the release of ACTH in response to immune signals, such as IL-1β and endotoxin (*Lee & Rivier* 1994, *Rivier* 1995, *Lee & Rivier* 1995, *Rivier* 1997). As in non-abusers, the stress response in alcohol abusers is further increased by a change to the upright position and exercise (*Eisenhofer et al* 1985), haemorrhage (*Elmér & Lim Jr* 1985, *Newsome Jr.* 1988, *Gruber et al* 1992), and injury and surgical intervention (*Newsome Jr.* 1988, *Tønnesen et al* 1992a, *Tønnesen et al* 1999b). The mechanism may include alcohol-induced oedema and swelling of the brain, as indicated by neuroprotection from furosemide (*Collins et al* 1998).

Not only alcohol intake, but also withdrawal, even for the short time during preoperative fasting, influences the stress level (chapter VI). The response in chronic abusers during acute intoxication remains to be described.

The human studies have several methodological flaws: small size, ill-defined study population and relation to withdrawal, and short sampling period. Neither in human nor in experimental studies has information been given about the hydration status, in spite of the well-known alcohol-induced blockade of anti-diuretic hormone, intravenous infusion of fluid, and/or transfusion of blood.

Our controlled surgical study dealing with possible mechanisms (*Tønnesen et al* 1992a) could be criticised for the small numbers of patients entered, the choice of design, and the intensive measurement of several parameters in the study period. However, the results of these asymptomatic alcohol abusers with respect to organ dysfunction were in line with previous and later studies in non-surgical patients, as mentioned above. Our controlled non-surgical study of the reversibility of immune suppression during abstinence from alcohol (*Tønnesen et al* 1992b) also suffered from a small material. However, suppressed delayed-type hypersensitivity was seen in all the alcohol patients on inclusion.

CONCLUSION

The data of the observational studies published hitherto indicate that through a diverse range of lesions alcohol abuse contributes to the development of alcoholic cardiomyopathy, thus making the heart more vulnerable to stress. A relation between the various lesions remains to be investigated.

Alcohol-induced immune incompetence includes dysfunction of the early phase of host defence against bacteria by reduced lymphocyte function, probably mediated by an altered cytokine balance. A direct interaction between ethanol and signalling proteins of the membrane may be part of the mechanism.

Haemostatic imbalance involves a reduced number of thrombocytes, owing to a toxic effect of alcohol on the bone marrow, reduced coagulation with inhibited release of thromboxane A_2 and B_2, and stimulated fibrinolysis.

An alcohol-induced increase in the activity of the HPA axis and the sympathetic activity is often followed by an adaptive feedback imbalance. Subsequently, the endocrine response may be exaggerated by exercise, trauma, and surgery.

VI. Pathophysiological mechanisms during and after operation

The haemodynamic changes occurring during major surgery include increased cardiac work and pulmonary resistance, owing to sympathetic stimulation (*Pavlin & Su* 1990). The preoperative subclinical insufficiency of the heart in alcohol abusers may not withstand the increased demand, thereby predisposing to such postoperative cardiac complications as arrhythmias and heart failure (*Tønnesen et al* 1987, *Felding et al* 1992, *Tønnesen et al* 1992a, *Spies et al* 1996).

Surgical trauma adds further to the alcohol-induced immune suppression. Major surgery down-regulates the T cell-directed immunoresponses, causing reduced delayed-type hypersensitivity (*Hammer et al* 1992), interleukin-2 expression, IFN production, T cell blastogenesis (*Faist et al* 1991), and cytolytic activity (*Deehan et al* 1995). Although these responses are partly similar to those induced by alcohol, the combined effect of alcohol and surgery accelerates immunomodulation. As a result, the preoperative, suppressed delayed-type hypersensitivity in the abuser is further reduced, thus leaving the patient with a poor postoperative immune competence, which is a possible mechanism of the increased infectious complications (*Tønnesen et al* 1992a).

In the retrospective study of transurethral prostatectomy, we found that the alcoholic patients had significantly more bacteriuria in routine postoperative cultures than had the matched controls (*Tønnesen et al* 1988). The groups did not differ with regard to bacterial species, which excludes the theory that alcohol abusers are infected by polymicrobial combinations or otherwise low-virulent species. Prophylactic antibiotic treatment was similar in the group of alcohol abusers and the matched control group (Table C in the appendix).

Surgical intervention interferes with haemostasis by initial activation of both coagulation and fibrinolysis followed by a depression of fibrinolysis postoperatively, thereby increasing the thrombo-embolic risk. A secondary increase in coagulation takes place between the third and the seventh day (*Rem et al* 1981, *Hawkey et al* 1983, *Sandset et al* 1989, *Sørensen et al* 1990, *Sørensen et al* 1992). A detailed analysis of the haemostatic activation by the combination of surgery and alcohol abuse remains to be performed.

Perioperatively, we found that the bleeding time in alcohol abusers is prolonged (*Tønnesen et al* 1992a), which may account for the increased risk of bleeding episodes (*Tønnesen et al* 1987, *Tønnesen et al* 1988, *Tønnesen et al* 1991, *Felding et al* 1992, *Sonne & Tønnesen* 1992, *Tønnesen et al* 1992a). A potential beneficial effect on thrombo-embolic complications is not measurable from the studies published hitherto, because of the small number of patients (*Tønnesen et al* 1987, *Tønnesen et al* 1988, *Tønnesen et al* 1991, *Felding et al* 1992, *Sonne & Tønnesen* 1992, *Tønnesen et al* 1992a, *Tønnesen et al* 1999b).

The stress response to trauma and surgery is increased by alcohol. In trauma patients, alcohol intoxication correlates to the plasma concentration of noradrenalin in a dose-dependent manner (*Newsome Jr.* 1988). An experimentally induced haemorrhage after alcohol intake was followed by a further increase in noradrenalin, but without the immediately up-regulation of the lowered blood pressure, which generally follows a bleeding episode (*Newsome Jr.* 1988). This indicates a delay of homeostasis, thus making the alcohol patient more vulnerable to perioperative bleeding. Animal studies of alcohol intoxication further report decreased mean arterial pressure, cardiac index, and left ventricular stroke work, together with protracted metabolic acidosis in the posthaemorrhagic phase (*Gruber et al* 1992). We found higher plasma concentrations of adrenalin, noradrenalin, and cortisol, and a higher heart rate and mean arterial pressure in alcohol abusers without intoxication as compared to non-abusers (*Tønnesen et al* 1992a), thus indicating increased activity of the SA system and HPA axis. The increased stress response may further increase the demands on an already dysfunctional organic system, thus adding to the risk of postoperative morbidity in alcohol abusers.

Other mechanisms may contribute to the increased postoperative morbidity in alcohol abusers. Although the preoperative nutrition index (*Simms et al* 1982) and the thickness of the triceps skin-fold did not differ in heavy alcoholics, moderate abusers, and abstainers (*Tønnesen et al* 1992b), impairment in the nutritional status of alcohol abusers often occurs. Alcohol-induced myopathy (*Sacanella et al* 1995) reduced the protein content in wounds (*Jørgensen et al* 1998) and the increased use of tobacco associated with consumption of alcohol (*Miller & Gold* 1998, *Møller et al* 2002) may also be part of the pathogenesis. Low activity in bone tissue may influence the outcome in orthopaedic surgery (*Lindholm et al* 1991).

The literature hitherto consists solely of observational studies. Our small study of surgical pathophysiology in alcohol abusers and matched controls (*Tønnesen et al* 1992a) points out some, but not all, of the possible mechanisms. Furthermore, the study is not useful for evaluation of associations between the pathophysiology and the clinical outcome, dose-response, or other subanalyses.

CONCLUSION

All the papers published hitherto concern observational studies. The mechanisms of alcohol-induced intra- and postoperative organ dysfunction may include factors such as subclinical cardiac insufficiency, immune incompetence, and haemostatic imbalance, which are already present preoperatively. The surgical stress response is greater in alcohol abusers, which may further compromise the already dysfunctioning organs, thus leading to the documented increase in postoperative morbidity.

VII. Prevention of the increased postoperative morbidity

A hypothetical step to reduce postoperative morbidity in alcohol abusers would be preoperative withdrawal from alcohol in due time before the surgical intervention. This hypothesis is based on the reversibility of the alcohol-induced organic dysfunctions during abstinence (Table III).

REVERSIBILITY OF ORGAN DYSFUNCTION AFTER ABSTINENCE

Several observational studies have addressed reversibility of organ failure after withdrawal from alcohol in non-surgical populations.

Recovery from acute and chronic myocardial failure in alcohol abusers after a period of total abstinence was described already in the sixties (*Brigden & Robinson* 1964), and several cases have since been reported. In about half the patients with severe heart failure, owing to alcoholic cardiomyopathy, the function improves and symptoms are reduced after one to six months of sobriety (*Teragaki et al* 1993, *La Vecchia et al* 1996, *Guillo et al* 1997), although the compensatory, dilated ventricle may persist (*Prazak et al* 1996). Reversibility seems to be correlated inversely to the severity of the histological changes (*Teragaki et al* 1993). The long-term prognosis for severe alcoholic congestive heart failure is rather good, compared to that for idiopathic dilated cardiomyopathy: the overall survival at ten years being 81% vs 30% (*Prazak et al* 1996), but only in patients who stop drinking (*Fauchier et al* 2000, *Gavazzi et al* 2000).

Subclinical cardiac insufficiency is mostly reversible after withdrawal. One month of abstinence normalises the ejection fraction of the alcohol abuser (*Kelbæk et al* 1987), although persistence of a low ejection fraction, which fails to increase appropriately at exercise, has been reported (*Cerqueira et al* 1991).

Abstinence from alcohol reverses the immunosuppression. Stem cells in the bone marrow of heavy drinkers regenerate within a few days (*Sullivan & Herbert* 1964). Functional reversibility is much slower, possibly because of the turnover of the circulating cells. It takes two weeks to improve the delayed-type hypersensitivity in alcohol abusers, and two months to normalise the response (*Tønnesen et al* 1992b). Alcohol-induced hyposplenism is reversible after one to six months of abstinence (*Corazza et al* 1997).

In an animal study, one week of abstinence protected the heart from sepsis-induced dysfunction (*McDonough* 1995). In contrast, other experimental studies have reported further depression of immunity during withdrawal, which is probably caused by the increased stress response (*Wu & Pruett* 1997). Human studies may support this, but they do not allow of sufficient interpretation. Thus, the patients were sober when tested, but the time between the last drink and sampling was not stated (*Stefanini et al* 1989, *Daniluk & Kandefer-Szerszen* 1994, *Cook et al* 1995, *Hrelia et al* 1995, *Uhlenbruck et al* 1995, *Ono et al* 1996, *Stefanini et al* 1996).

Alcohol withdrawal may be followed by a rebound phenomenon, a markedly increased platelet aggregation, especially that induced by thrombin (*Fink & Hutton* 1983, *Hillbom et al* 1985, *Arai et al* 1986, *Mikhailidis et al* 1986, *Rand et al* 1990). The rebound phenomenon may theoretically provoke thrombo-embolic disease in the early period of abstinence from alcohol, but no valid clinical data are available. The platelet count, thromboxane release, bleeding time, and aggregation are all normalised within one to four weeks of abstinence (*Hillbom et al* 1985, *Arai et al* 1986, *Neiman et al* 1987), which possibly reflects the half-life of circulating thrombocytes. The duration of alcohol-induced fibrinolytic activation seems shorter, but the mechanism has not been evaluated (*Hendriks et al* 1994).

Six months of abstinence improves the reduced activity in bone tissue (*Lindholm et al* 1991) and in two months the protein content in wounds is normalised (*Jørgensen et al* 1998).

Cessation of alcohol intake is associated with over-activity of the sympathetic nervous system. The activity of the SA system is highest during the first day of withdrawal (*Smith et al* 1990), and is related to changes in the ST segment on the electrocardiogram and an increase in myocardial enzymes (*Denison et al* 1997). The plasma concentration of noradrenalin fluctuates with the severity of the withdrawal symptoms (*Smith et al* 1990). Hypercortisolaemia disappears within a week of abstinence (*Linnoila* 1987, *Adinoff et al* 1991).

Impairment of the response to hyperthermic, psychosocial, and exercise stress is still demonstrable after two to seven weeks of abstinence (*Eisenhofer et al* 1985, *Vescovi*

Table III. *Time required for improvement of organic dysfunction after abstinence from alcohol.*

Cardiac function	
with severe failure (*La Vecchia et al* 1996, *Guillo et al* 1997, *Teragaki et al* 1993)	1-6 months
without symptoms (*Kelbæk et al* 1987)	< 1 month
Immune competence (*Tønnesen et al* 1992b)	2-8 weeks
Haemostasis (*Hilbom et al* 1985, *Neiman* 1987, *Arai et al* 1986)	1-4 weeks
Stress response (*Linnoila* 1987, *Ehrenreich et al* 1997, *Tønnesen et al* 1999b)	2-12 weeks
Wound healing (*Jørgensen et al* 1998)	< 2 months
Bone regeneration (*Lindholm et al* 1991)	< 6 months

et al 1997, *Lovallo et al* 2000), but the response to multifaceted stress test is normalised within 12 weeks (*Ehrenreich et al* 1997).

PREOPERATIVE ALCOHOL ABSTINENCE

As abstinence from alcohol seems to improve the function of several organ systems, we investigated the potential effect of a prophylactic intervention on postoperative morbidity. In a randomised clinical trial, we studied the influence of one month of preoperative withdrawal under disulfiram control versus continuous drinking.

One month of abstinence prior to surgery was chosen as a compromise between a short waiting time for patients with colorectal cancer scheduled for surgery and the time needed for preoperative abstinence. On the one hand, the guidelines for cancer surgery recommended that diagnosis and indication for surgery should be made within two weeks of admission to hospital and that the surgical procedure should be performed within another two weeks. On the other hand, three months of abstinence prior to surgery seemed preferable for normalising most of the organ failures. However, one month would allow most of the dysfunctions to improve, but not to become normal, and inclusion of the patients on admission would not prolong the preoperative waiting time significantly. Disulfiram was chosen as a supplement to help preoperative abstinence in the intervention group. The intervention was performed in co-operation with the Copenhagen Alcohol Units and in accordance with their guidelines.

We found that one month of withdrawal significantly improved preoperative delayed-type hypersensitivity response (37 mm^2 vs 12 mm^2) and reduced signs of myocardial ischaemia on a Holter tape recording (23% vs 74%). Surgical stress response, assessed on the heart rate, catecholamines, and IL-6, was significantly lower in the intervention group, whereas there was no difference in the mean arterial pressure, serum cortisol, or plasma glucose. Postoperatively, the intervention group also developed significantly less myocardial ischaemia (23% vs 85%), arrhythmia (33% vs 86%), and nocturnal hypoxaemic episodes (4 vs 18).

Five of the 16 patients in the intervention group and 14 of the 19 drinking patients developed complications requiring treatment after elective colorectal resection ($p = 0.02$). Two of 16 vs eight of 19 had major complications ($p = 0.07$), and four of 16 vs 11 of 19 had minor complications ($p = 0.09$). The most common complications in the drinking group were wound complications with or without fascial rupture, pneumonia, and cardiopulmonary insufficiency requiring intensive care.

The high morbidity in the continuous drinkers is comparable to previous results reported in alcohol abusers (*Tønnesen et al* 1987, *Tønnesen et al* 1992a), and the morbidity in the intervention group is consistent with studies of unselected patients undergoing conventional colorectal surgery (*Bokey et al* 1995, *Hansen et al* 1996, *Leung et al* 1997, *Vignali et al* 1997). In our study, all complications were registered. No differentiation was attempted with regard to surgery-related complications (i.e. side effects) and adverse events (*Pedersen et al* 2001).

Although the organic dysfunctions were not completely reversed after one month of abstinence, this period seems long enough to benefit alcoholic patients.

Our study can be criticised for the small population and, although the two groups were comparable in major preoperative characteristics, minor differences between the groups may have existed. For instance, the intervention group may have changed their life-style in other ways, which were not monitored. Moreover, the patients were recruited from three centres over a long period and this may have increased the variation between the groups. Other flaws are the non-blind design, internal data monitoring, and many exclusions, owing to cancelled or delayed surgery or endoscopic procedures (7/42). The small study population did not permit interesting subanalyses, such as dose-response between the DTH reaction and postoperative infection. Furthermore, the combination of the small material and the high compliance excludes subanalytical comparison of alcohol reduction with abstinence and a continuously high intake. Risk of type 1 failure was present and could be overcome by repeating the investigation. As this is the first randomised clinical study of preoperative intervention in alcohol abusers undergoing surgery, confirmation from other studies is needed before final recommendations can be made.

PREOPERATIVE REDUCTION IN ALCOHOL INTAKE

The effect of reduction instead of complete abstinence from alcohol before surgery is unknown. According to an indication that there is a dose response between alcohol intake and postoperative outcome (*Sørensen et al* 1999, *Felding et al* 1992, *Spies et al* 1996), one could speculate about the hypothetical effect.

Reduction may prolong the recovery phase of the organ dysfunction, owing to the continuous induction by a small alcohol dose. On the other hand, a small intake throughout the day may prevent abstinence stress, which, per se, suppresses several bodily functions. The hypothetical effect of reduction is based on determination of a threshold value/dose response of alcohol intake in relation to outcome. A reduction study should not include alcohol-dependent patients, who are characterised by their loss of control over drinking and inability to cut down.

CLINICAL GUIDELINES FOR ALCOHOL AND SURGERY

Further randomised studies and meta-analyses are needed for final recommendations, but, in the meantime, clinical guidelines, based on the present evidence and the best clinical practice for surgery and alcohol are required. The latter includes general information, systematic identification, and intervention, meaning that all hospital patients drinking more than 21 drinks per week for men and 14 for women should receive intervention according to their needs and wishes (*Becker & Kann* 2001).

The question is therefore not whether or not surgical patients should be offered alcohol prevention. Today, nearly all surgical departments in Denmark include alcohol history in the preoperative routine. However, it is seldom followed up by intervention (*Møller & Tønnesen* 2001). Only very heavy drinkers are usually admitted to treatment before surgery, because experience shows that heavy drinking or severe withdrawal syndrome interferes with the postoperative rehabilitation programme. The important question is where in the surgical patient's way through hospital alcohol intervention should be integrated, before or after the operation.

Preoperative alcohol intervention seems preferable, compared to postoperative treatment: By preoperative intervention the chance of improved surgical outcome is higher, the risk of postoperative alcohol withdrawal symptoms is lower, and the cost of intervention in the outpatient clinic is lower than the resources required for postoperative treatment in the department.

Preoperative intervention is supported by the high motivation for changes in life-style before surgery, as measured by a surprisingly high compliance (*Tønnesen et al* 1999b, *Møller et al* 2002). Furthermore, today the preoperative ambulatory contact is often of longer duration than the scheduled hospital stay, whereas most surgical patients have no postoperative visits in the outpatient clinic. The ambulatory period is used for diagnostic procedures and preparation for surgery, and time spent waiting for the operation. Patient information is naturally given before surgery. The routine information should include the high postoperative morbidity in alcohol abusers and the potential effect of preoperative abstinence.

Preoperative abstinence for at least four weeks before surgery is therefore preferable to postoperative intervention. However, in order to control for a minor risk of integrating a useless procedure, implementation should be followed by monitoring of the effect in the clinical databases available at the departments.

CONCLUSION

Withdrawal from alcohol reverses organic dysfunction in non-surgical patients. Haemostasis normalises after one to three weeks, cardiac function after one month, immune function after two months, and response to external stress after three months. Accordingly, one small randomised investigation has shown that one month of abstinence before surgery improves several organic dysfunctions and reduces postoperative morbidity. The study has methodological flaws, so further studies are required before final recommendations can be given. In the meantime, clinical guidelines are required. From the few side effects of intervention, the poor spontaneous outcome, the relatively low risk of type 1 failure compared with the change to a beneficial effect, and the current patient pathway, the guidelines should include information and support for four weeks of preoperative abstinence. The effect of alcohol reduction instead of complete withdrawal is unknown.

VIII. Other life-style risk factors that impair the postoperative outcome

Several other preoperative life-style factors influence the outcome after surgery. Smoking is now considered a major risk factor. Although postoperative morbidity is increased to a lesser degree than in alcohol abusers (*Sørensen et al* 1999, *Stopinski et al* 1993), smoking is more common in the population and in surgical patients. The first randomised clinical study in this field shows that six to eight weeks of cessation of smoking has a significant effect on complication after hip and knee prosthetic surgery, whereas a reduction in smoking to less than 50% does not influence the postoperative morbidity (*Møller et al* 2002).

Malnutrition is a well-known risk factor. However, even patients with a normal nutritional status benefit from early intervention (Beier-Holgersen & Boesby 1996), which probably prevents damage induced by the surgical catabolic response, postoperative anorexia, and the preoperative underlying disease (*Silk & Green* 1998). A concomitant increase in physical activity may further reduce the weight loss and muscle fatigue that often follow surgery (*Christensen* 1995).

Coincidence of life-style risk factors seems to act synergistically on the surgical outcome (*Schwilk et al* 1997). Intended mono-intervention against alcohol and smoking, and to improve nutrition (*Tønnesen et al* 1999b, *Møller et al* 2002, *Beier-Holgersen & Boesby* 1996) seems to improve the postoperative outcome significantly. But abstinence from alcohol may also change other habits positively, for instance an improved caloric intake, reduced smoking, as well as better social functioning. Furthermore, the intervention group may receive more professional attention and psychosocial support by the enthusiastic researchers in the investigational period, thereby increasing the chance of a better outcome.

Other confounders may be a positive effect of minor alcohol consumption in the control group, according to the J-shaped curve known from other fields of clinical alcohol research (*Grønbæk et al* 1995). Alcohol preference has not been evaluated in surgical studies, although the literature gives the hypothesis that wine drinkers are less vulnerable to the development of alcohol-related disorders, such as cancer of the upper digestive tract (*Grønbæk et al* 1998) and hip fractures (*Høidrup et al* 1999). This positive effect of wine may, however, reflect fundamental differences in the life-style of wine drinkers and other alcohol abusers, as addressed in a recent Danish study (*Tjønneland et al* 1999).

IX. Conclusion

Up to the present, thirty observational studies and one minor randomised clinical trial (including those of the author and co-workers) have evaluated the association between alcohol abuse and postoperative outcome. Several of the studies are small, use retrospective and/or case-control designs, give a sparse definition of alcohol abuse or complications, apply simple statistical procedures without confounder control, or have other methodological flaws. A meta-analysis cannot be performed until more clinical randomised investigations have been published. However, the results of the studies are in line, showing evidence of an association between alcohol abuse and increased postoperative morbidity. The personal and economic consequences are tremendous.

We found that the most frequent complications seen are infections, cardiopulmonary insufficiency, and bleeding episodes. Our studies pointed out some possible mechanisms, which included suppressed immune capacity, subclinical cardiac insufficiency, and prolonged bleeding time before surgery, as well as increased stress-response intraoperatively. The suggested mechanisms were not analysed for correlation to the complications. Nor was the dose-response evaluated.

Our small randomised study demonstrates that prevention is possible. Four weeks of abstinence before surgery improves the organic dysfunctions and reduces postoperative morbidity significantly.

Further studies are required for final recommendations, but, in the meantime, clinical guidelines for alcohol abusers undergoing surgery should include up-to-date patient information and four weeks of abstinence before surgery, in accordance with the evidence-based association, the potential prevention attained by preoperative abstinence, and the best clinical practice. Alcohol is one among other risk factors of importance for the surgical outcome. These risk factors, however, are preventable by early intervention, such as smoking cessation, nutritional support, and psychosocial support.

X. Future strategy

General prevention in relation to alcohol is especially important in Denmark, because of our relatively high morbidity and mortality from alcohol-related diseases (*Juel* 2001). Prevention should be available in all relevant arenas, including hospitals, so as to reduce harmful intake and subsequent physical, psychological, and social disorders.

Today, prevention and health promotion involve interdisciplinary measures at many hospitals, primarily by medical doctors and nurses. However, these measures only reach a minor part of the patients (*Træden et al* 2001).

In future, all patients admitted to surgery should be offered a dialogue on prevention with the surgeon, anaesthesiologist, general practitioner, or other health professionals, which focuses on risk factors in relation to the operative treatment, diagnosis, and prognosis. The dialogue should include motivational counselling, suggestions for risk reduction, and supportive intervention, in accordance with the wishes and requirements of the patients. Processes of change in human have been described and related tools have been developed for use in clinical daily life. (*Prochaska & DiClemente* 1983, *Iversen* 1998, *Mundt et al* 2001, *Kann et al* 2001).

Alcohol-related disorders are widespread and lead to poorer outcome after surgery. However, in addition to a long-term health gain through preventive procedures, surgical patients appear to benefit from only four weeks of preoperative abstinence from alcohol. Withdrawal before treatment may hypothetically improve the outcome in stressful procedures other than surgery, for instance radiation therapy, which it would seem relevant to evaluate in the future.

MULTI-MODAL PREVENTION IN SURGERY

Alcohol abuse is one among other life-style risk factors of relevance to the postoperative outcome. Nutritional intervention was introduced several years ago (*Silk & Green* 1998), psychosocial intervention, including education and empowerment of the patient, improves the outcome (*Egbert et al* 1964, *Daltroy et al* 1998), and preoperative smoking cessation is a new objective for action (*Møller et al* 2002). The preventive effect of physical exercise on the development of complications after surgery is being addressed in ongoing studies. However, the risk factors are related to some degree and may occur simultaneously. Investigation of a multi-factorial preventive programme in the preoperative period thus seems appropriate.

Furthermore, high-risk alcohol abusers would possibly also benefit from fast-track surgery, which combines various techniques in patient care during and after surgery (*Kehlet & Mogensen* 1999, *Basse et al* 2000). This focuses

on reducing intraoperative stress by using regional anaesthesia and minimal invasive, normothermic surgery, and improving postoperative care with effective pain relief, prophylaxis for nausea and vomiting, early mobilisation, oral nutrition, and minimal use of tubes, drains, and catheters. Preliminary data from non-randomised studies are positive (*Wilmore & Kehlet* 2001). It seems relevant to evaluate fast-track surgery in alcohol abusers undergoing subacute or even emergency procedures in a clinical randomised design.

Hypothetically, a complete multi-modal perioperative programme would, however, be most fruitful and this should be evaluated in alcohol abusers scheduled for elective surgery, thus combining preoperative multi-factorial prevention and fast track surgical intervention during and after surgery.

Although, it would not reduce postoperative morbidity, alcohol abusers admitted for emergency operations should be offered intervention afterwards, in order to reduce their alcohol intake (*Antti-Poika et al* 1988, *Gentilello et al* 1999).

BARRIERS TO ALCOHOL PREVENTION

Prevention and health promotion have become part of the obligations of Danish hospitals through laws passed in 1995 and 2001 (*Danish Ministry of Health* 1995, *Danish Ministry of Health* 2001). This is also incorporated in the rules for new medical specialists, as described by Commission of Specialists (*Commission of Specialists* 2000).

However, information to and training of health professionals are necessary to meet this obligation, as well as for overcoming the major barrier of ourselves (*Willaing et al* 2001), the moderate barrier of the organisation (*Fredslund* 2001), and the minor barrier of the patients (*Møller & Villebroe* 2002). The organisational barriers include priority of alcohol intervention in hospital, which has been established in only about half the Danish hospitals (*Træden et al* 2001).

Integration of prevention in clinical daily life is a challenge to the staff and the organisation. It is therefore promising to note that about half the surgical departments have a positive attitude to the diagnosis of and intervention in a high alcohol intake. Furthermore, one-third would be interested in taking part in future investigations of this issue (*Møller & Tønnesen* 2001).

XI. Summaries

Patients who drink too much have more complications after surgery. The aim of this thesis was to evaluate the evidence, possible mechanisms, and prevention of the increased postoperative morbidity in alcohol abusers, defined by a consumption of at least five drinks per day.

The literature could be criticised for several methodological flaws. Nevertheless, the results are in agreement showing moderate to strong evidence of increased postoperative morbidity after surgical procedures on alcohol abusers. There is weak to moderate evidence of increased postoperative mortality, hospital stay, and re-operation. The personal and economic consequences are tremendous. The incidence of alcohol abusers undergoing surgery was 7% to 49%, according to gender and diagnosis. They have been identified by a self-reported alcohol intake, which implies the possibility of underestimation.

Alcohol markers could be used for a more precise identification of alcohol abuse. However, the inability of the questionnaires to detect short-term changes in intake and abuse without dependence, the inconsistent predictive values of the biological markers, and the lack of evidence of an association to postoperative morbidity reduces their usefulness. A detailed alcohol history is therefore recommended.

The pathophysiology may include alcohol-induced organ dysfunctions. We demonstrated that subclinical cardiac insufficiency, immune incompetence, and haemostatic imbalance were already present preoperatively. A relation between the various lesions remains to be investigated. The surgical stress response was greater in alcohol abusers, which may further compromise the already dysfunctioning organs, thus leading to the documented increase in postoperative morbidity.

Withdrawal from alcohol reverses organic dysfunction in non-surgical patients. Haemostasis normalises after one to four weeks, cardiac function after one month, immune function after two months, and response to external stress after three months. Accordingly, our small randomised investigation has shown that one month of abstinence before surgery improves several organic dysfunctions and reduces postoperative morbidity. We have demonstrated that prevention before surgery is possible. The study has methodological flaws, so further studies are required before final recommendations can be given.

However, in the meantime clinical guidelines for alcohol abusers undergoing surgery should include up-to-date patient information and four weeks of abstinence before surgery, in accordance with the evidence-based association, the potential prevention attained by preoperative abstinence, and the best clinical practice. Implementation should be monitored in the clinical databases.

In future, all patients admitted to surgery should be offered a health promoting dialogue with the surgeon, anaesthesiologist, general practitioner, or other health professionals, which focuses on alcohol among other risk factors in relation to the operative treatment, diagnosis and prognosis. A beneficial effect attainable from this multi-modal prevention and fast track surgery should be investigated among the alcohol abusers.

DANISH SUMMARY

Patienter, der drikker for meget, har flere komplikationer efter kirurgi. Formålet med denne oversigt er at evaluere evidensen, mulige mekanismer og forebyggelse af den øgede postoperative morbiditet blandt alkoholpatienter, som er definerede ved et forbrug på mindst fem genstande dagligt.

Litteraturen kan kritiseres for metodologiske problemer. Ikke desto mindre viser resultaterne samstemmende moderat til stærk evidens for øget postoperativ morbiditet efter operation af alkoholpatienter. Der er svag til moderat evidens for øget postoperativ mortalitet, indlæggelsesvarighed og reoperation. Dette har store personlige og økonomiske konsekvenser. Alkoholpatienterne udgør 7-49% af operationspatienterne, afhængig af køn og diagnose. De er identificeret ved selvrapporteret alkoholforbrug, hvilket medfører risiko for underrapportering.

Alkoholmarkører i form af spørgeskemaer og biologiske markører kunne synes anvendelige til en mere præcis identifikation af alkoholmisbrug. Imidlertid er disse ikke så brugbare, da kortere tids ændringer i forbruget eller overforbrug uden afhængighed ikke kan identificeres ud fra spørgeskemaerne, og da de biologiske markører har stor variation mht. prædiktive værdier. Desuden mangler dokumentation for en sammenhæng mellem markørerne og postoperativt outcome. Derfor anbefales en detaljeret alkoholanamnese indtil videre.

Årsagen til de mange postoperative komplikationer skal formentlig søges i alkoholinduceret organdysfunktion. Vi har påvist subklinisk hjerteinsufficiens, nedsat immunkompetence og forlænget blødningstid hos alkoholpatienter allerede inden operationen. En eventuel sammenhæng mellem de forskellige organpåvirkninger mangler at blive undersøgt. Per- og postoperativt udvikler alkoholpatienterne et abnormt højt stressrespons, som yderligere kan forværre de dysfungerende organsystemer.

Blandt ikke-kirurgiske alkoholmisbrugere er organdysfunktionen reversibel efter total afholdenhed. Hæmostasen normaliseres efter 1-4 uger, hjertefunktionen efter en måned, immunkapaciteten efter 2 måneder og reaktion på eksternt stress efter 3 måneder. I et mindre randomiseret klinisk studie har vi tilsvarende fundet, at blot en måneds afholdenhed inden større kirurgi forbedrer flere organdysfunktioner og reducerer den postoperative morbiditet. Vi har samtidig demonstreret, at præoperativ afholdenhed er gennemførlig. Studiet har flere metodologiske problemer, og endelige anbefalinger kræver yderligere studier.

I mellemtiden er det nødvendigt med kliniske retningslinjer for alkoholpatienter, som skal opereres. Retningslinjerne bør indeholde en opdateret information med forslag om 4 ugers afholdenhed inden operation, i overensstemmelse med den evidensbaserede association, den potentielle forebyggelse ved ophør med alkoholindtagelse og den bedste kliniske praksis. Implementeringen skal monitoreres i en klinisk database.

Fremover bør alle patienter inden eventuel operation tilbydes en forebyggelsessamtale med fokus på alkohol samt andre risikofaktorer, der har betydning for den kirurgiske behandling, diagnose og prognose. En eventuel effekt af en sådan multimodal intervention kombineret med et accelereret patientforløb bør fremover gøres til genstand for undersøgelse blandt de kirurgiske højrisikopatienter, der drikker for meget.

XII. References

In the reference list ø and ö are listed under o; æ, ä, and å under a; ü under u.

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Table A in the appendix. *Complications after surgery in alcohol abusers compared with control patients.*

General surgery	Country Study year	Evidence	Design	Total no pts.	No alc pts.	Alcohol categories	Asymptom-atic alc.pts.	Inclusion criteria/ operation	Outcome measurement	Analysis	Cofounder control	Results	Odds ratio morbidity	Odds ratio mortality	Second surgery
Felding (1992)	Denmark (1982-88)	3b	Cohort P	229	15	≥5 drinks/day 3-4 drinks/day ≤2 drinks/day	Unknown	Elective hysterectomy	Mortality Morbidity	Chi^2 test	No	≥5 drinks/day: 80% compl 3-4 drinks/day: 27% ≤2 drinks/day: 13%	26.6 (7.0-100.5)	(No mortality)	Unknown
Kim (1974)	USA (1968-71)	4	Cohort R	135	19	Heavy drinking vs not heavy drinking (no criteria)	No (2 pts with cirrhosis)	Gastric re-section due to life-threatening haemorrhage	Incidence of heavy drinkers in surviving and dead pts.	No	No	27% alc in the dead group vs 10% in the survival group	———	3.5 (1.3-9.5)	———
Klotz (1994)	Germany (1988-90)	2b	Cohort P	682	49	>20 g alc/day vs < 20 g alc/day	Unknown	General surgery	Morbidity	Multiple logistic regression	Malignancy, COL, car-diac history, ethnicity, hepatosple-nomegaly, old age, hypertension, haematocrit <40	Alc significant risk factor	(Significant but not calcul-able from the article)	———	———
Marcantonio (1994)	USA (1990-92)	2b	Cohort P	876	40	Alc abuse vs non-abuse (criteria given, excl previous delirium)	Unknown	Non-cardiac surgery, age ≥50 years	Risk factors for delirum	Multiple logistic regression	Age, activity and cognitive status, preop. electrolytes, operation	3.3 (1.4-8.3)	3.3 (1.4-8.3)	———	———
Pittet (1993)	Switzerland (1984-88)	2b	Cohort R	176 (of 5457)	37	>80 g alc/day vs <80 g alc/day	No (6 pts. with cirrhosis)	Sepsis after all kinds of surgery	Mortality	Multiple logistic regression	Age, sex, elective, diagnosis, surgery, comorbidity, ISS and Apache score	1.4 (0.9-2.1)	———	1.4 (0.9-2.1)	———
Rantala (1997)	Finland (1988-90)	2b	Cohort P	43 (of 772)	20	Alc abuse vs non-abuse (criteria given)	Unknown	Wound infection after general surgery	Risk factors for wound infection	Multiple logistic regression	Age, activity chr. disease, nutrition, status, ASA, op.time malignancy	Alc abuse, wound contamination, long operation sign risk factors	(Significant but not calcul-able from the article)	———	———
Sørensen (1999)	Denmark (1993-96)	2b	Cohort P/R	333	8	1-7 drinks/week 8-14, 15-21, 22-35, > 35	Unknown	Colorectal resection	Risk factors for anasto-motic leakage	Multiple logistic regression	Age, sex, charge of surgeon, operation, tobacco	>35drinks/days vs 1-7: 7.18 (1.20-43.01)	7.18 (1.20-43.01)	———	———

Table A in the appendix continues.

Table A in the appendix continued.

General surgery	Country Study year	Evidence	Design	Total no pts.	No alc pts.	Alcohol categories	Asymptom-atic alc.pts.	Inclusion criteria/ operation	Outcome measurement	Analysis	Cofounder control	Results	Odds ratio morbidity	Odds ratio mortality	Second surgery
Spies (1996)	Germany (unknown)	3b	Cohort P	213	121	≥5 drinks/day and pos CAGE (3-4 drinks/day) ≤2 drinks/day and neg CAGE	Unknown	Upper aero-digestive tract resec-tion	Mortality Pneumonia and sepsis	ANOVA, Kruskal-Wallis, Chi^2 test	No	7% mortality vs 0% (p= 0.04) 38% pneumonia vs 0% (p=0.001), 13% spesis vs 0% (p=0.001)	All compli-cations 19,6 (6.6-57.4)	24.5 (1.4->100)	2.1 (0.7-6.7)
Stopinski (1993)	Germany (1988-91)	3b	Cohort P	213	15	>60 g alc/day vs <60 g alc/day	Unknown	Inguinal hemiotomy, cholecyst-ectomy, colorectal resection	Infection (wound, urinary in-fection, pneumonia)	Chi^2 test	No	60% infection vs 16% (p<0.01)	8.1 (2.7-24.3)	———	———
Tønnesen (1999b)	Denmark (1996-98)	1b	RCT P	20+22	42	≥5 drinks/day randomised to abstinence vs routine	Yes	Elective colorectal resection	Mortality Morbidity	Fisher's exact test	Randomisation, stratification reg. department and colonic or rectal resection	11% mortality vs 6% (p=0.5) 74% compl vs 31% (p=0.02)	6.2 (1.4-26.8)	1.8 (0.1-22.2)	3.8 (0.9-15.4)
Tønnesen (1992a)	Denmark (1986-89)	2a	Case-Control P	2×16	16	≥5 drinks/day and pos MAST ≤2 drinks/day and neg MAST	Yes	Elective colorectal resection	Morbidity	Fisher's exact test	Pair-matched: age, sex, weight, tobac-co, diagnosis, chr. diseases, operation	67% compl vs 20% (p=0.04)	8.0 (1.5-42.1)	———	———
Tønnesen (1988)	Denmark (1979-83)	3a	Cohort R	2×73	73	≥5 drinks/day vs ≤2 drinks/day	Yes	Transurethral resection of prostate	Mortality Morbidity	Chi^2 test	Pair-matched: age, sex, weight, tobac-co, diagnosis, chr. diseases, operation	0% mortality vs 0% (p=1.0) 62% compl vs 20% (p<0.01)	6.2 (3.0-12.9)	(No mortality)	5.1 (1.4-18.4)
Tønnesen (1987)	Denmark (1976-84)	3a	Case-Control P	2×32	32	≥5 drinks/day vs ≤2 drinks/day	Yes	Elective colorectal resection	Mortality Morbidity	Chi^2 test	Pair-matched: age, sex, weight, tobac-co, diagnosis, chr. diseases, operation	16% mortality vs 3% (p=0.08) 75% compl vs 34% (p<0.01)	5.7 (1.9-16.8)	5.7 (0.6-51.8)	3.2 (0.9-11.5)
Weigelt (1992)	USA (1983-89)	2a	Cohort P	1468	Unknown	Alcohol abuse recorded by the surgeon	Unknown	General sur-gery, trauma, thoracic and transplant service	Wound infection	Multiple logistic regression	Contamination, operation, obesity and postoperative stay	OR 1.58 (1.09-2.30)	1.6 (1.1-2.3)	———	———

Orthopaedic surgery	Country Study year	Evidence	Design*	Total no pts.	No alc pts.	Alcohol categories	Asymptom-atic alc.pts.	Inclusion criteria/ operation	Outcome measurement	Analysis	Cofounder control	Results	Odds ratio morbidity	Odds ratio mortality	Second surgery
Antti-Polka (1988)	Finland (1984-85)	3a	Cohort P	285	88	Pos MAST (probable alc. abuse) vs Neg MAST	Unknown	Osteosynthe-sis of ankle fracture	Mortality Morbidity	Chi^2 test	No	1% mortality vs 1% (p=1.0) 17% compl vs 9% (p=0.05)	2.0 (1.0-4.3)	(No mortality)	———
Hedlundh (1995)	Sverige (1988-90)	3b	Case-Control R	178	M: 10 W: 3	Suspected abuse vs no suspection	Unknown	Dislocation matched to no disloca-tion after hip replacement	Incidence of suspected abuse in the two groups	Chi^2 test	Matched: age, sex, operation year, diagnosis	Suspected abuse more often in the dislocated group	M: 4.4 (1.4-14.6) W: 0.9 (0.7-3.5)	———	———

Isaacs (1994)	Canada (1990-91)	3b	Cohort R	27 (of 215)	Unknown	Alcohol abuse vs non-abuse (no criteria)	Unknown	Bleeding complications after hip fracture repair	Risk factors associated with bleeding	Multiple logistic regression	Age, sex, med., dementia, TE event, fracture, surgery, anticoag.	Alc abuse, dysreg. AC treatment were risk factors	(Significant but not calculable from the article)	———	———
Laxenaire (1979)	France (Unknown)	3b	Cohort P	54	Unknown	Alcoholism vs non-alcoholism	Unknown	Lung operation	Risk factors associated with infection	Chi^2 test	No	Alcoholism was associated with infections	(Significant but not calculable from the article)	———	———
Poon (1994)	Australia (1992)	3a	Cohort P	94	34	Pos AUDIT vs Neg AUDIT	Unknown	Orthopaedic surgery	Morbidity and hospital stay	Chi^2 test and Fischer exact test	No	47% vs 22% compl 11.2 vs 9.2 days	3.2 (1.3-8.0)	———	———
Tønnesen (1991)	Denmark (1977-88)	3a	Case-Control R	2×90	90	≥5 drinks/day vs ≤2 drinks/day	Yes	Osteosynthesis of ankle fracture	Morbidity	Chi^2 test	Pair-matched: age, sex, weight, tobacco, diagnosis, chr. diseases, operation	0% mortality vs 0% (p=1.0) 33% compl vs 9% (p<0.01)	5.1 (2.2-11.8)	(No mortality)	4.1 (1.7-10.1)

Thoracic surgery Country Study year	Evidence	Design*	Total no pts.	No alc pts.	Alcohol categories	Asymptomatic alc.pts.	Inclusion criteria/ operation	Outcome measurement	Analysis	Cofounder control	Results	Odds ratio morbidity	Odds ratio mortality	Second surgery
Larsen (1978) Norway (1971-76)	3b	Cohort R	110	11	Exc. consumption vs non-consumption (no criteria)	Unknown	Aortic valve replacement	Mortality	No	No	73% vs 8%	———	(30.3) (6.7-137.5)	———
Maxson (1999) USA (1997)	3b	Cohort P	321	31	Pos CAGE (probable alc. abuse) Neg CAGE)	Unknown	Elective vascular and thoracic procedures	Complications and delirium (wound compl not reg.) ICU and hospital stay	Fisher's exact test	No	CAGE pos: 10% compl. + 13% delir. More readm. CAGE neg: 11% + 1% delir	2.0 (0.8-5.0)	———	———
Neuenschwander (2002) Denmark (1997-98)	3a	Cohort R	107	13	≥5 drinks/day vs <5 drinks/day	Unknown	Intended curative resection for lung cancer	Mortality Morbidity	Multiple logistic regression	Sex, age, smoking, pulm. function, chr. disease, transfusion, bleeding	23% mortality vs 2% 54% morbitity vs 33%	1.6 (0.7-17.7)	13.8 (2.1-92.7)	———
Roach (1996) USA (1991-93)	2b	Cohort P	2417	198	Exc. consumption vs non-exc. consumption (no criteria)	Unknown	Coronary bypass	Adverse cerebral outcome: Type I (major) Type II (minor)	Multiple logistic regression status, operative procedures	Old age, medical history incl cardiac (1.3-5.5)	Type II, (but not I) 2.6	2.6 (1.3-5.5)	———	———
Wolman (1999) USA (Unknown)	2b	Cohort P	273	3	Alc. abuse vs no abuse	Unknown	Intracardiac surgery and coronary bypass	Adverse cerebral outome: Type I (major) Type II (minor)	Multiple logistic regression	Old age, medical history incl cardiac status, operative procedures	Type II, (but not I) 6.4 (1.4-29.0)	6.4 (1.4-29.0)	———	———

Table A in the appendix continues.

Table A in the appendix continued.

Plastic surgery	Country Study year	Evidence	Design*	Total no pts.	No alc pts.	Alcohol categories	Asymptom-atic alc.pts.	Inclusion criteria/ operation	Outcome measurement	Analysis	Cofounder control	Results	Odds ratio morbidity	Odds ratio mortality	Second surgery
Pelczar (1993)	USA (1990-91)	2b	Cohort P	119	39	Present abuse and Pos CAGE vs Neg CAGE	Unknown	Extended cancer surgery in head and neck	Predictors of compli-cations	Multiple logistic regression	Age, sex, tumor, cancer stage, ASA, hypertension, smoking	Poor functional capacity, alcohol abuse, elevated WBC, prolonged surgery of signif-icance	(Significant but not calcul-able from the article)	———	———
Shindo (2000)	USA (1992-97)	3b	Cohort R	53	12	Heavy alcohol use vs non-heavy use (no criteria)	Unknown	Fibula osteo-cutaneous flap in head and neck re-construction	Donor site complica-tion	Fisher's exact test	No	42% alc and 23% non-alc had compl.	2.4 (0.6-9.12)	———	———
Neurological surgery	Country Study year	Evidence	Design*	Total no pts.	No alc pts.	Alcohol categories	Asymptom-atic alc.pts.	Inclusion criteria/ operation	Outcome measurement	Analysis	Cofounder control	Results	Odds ratio morbidity	Odds ratio mortality	Second surgery
De-Mol (1985)	Belgium (1975-82)	3b	Cohort R	63	11	Alcoholism vs non-alcoholism	Unknown	Hydroceph-alus (normal pressure)	Complica-tions	Chi^2 test	Unknown	81% alc vs 40% had compl.	6.6 (1.6-33.9)	———	———
Klekamp (1999)	USA (1989-95)	3b	Case-Control R	2×35	7	Alcohol abuse vs non-abuse (no criteria)	Unknown	Methicillin-resistant sta-phylococcal wound infec-tions requir-ing operative debridement	Risk factors for wound infection after spinal surgery	Multiple logistic regression	Sex, age, to-bacco, lympho-penia, WBC, chr. infection, steroids, pro-tein	Alc was asso-ciated with all kinds of infec-tions	(Significant but not calcul-able from the article)	———	———
Mellergård (1996)	Sweden (1969, 1979 1983, 1993)	3b	Cohort R	218	32	Alcoholics vs non-alcoholics (no criteria)	Unknown	Operation for chronic sub-subdural haematoma	Re-opera-tion	Chi^2 test	No	No significant risk factors for re-op. (19% alc vs 13% non-alc)	———	———	1.6 (0.6-4.1)
Sonne (1992)	Denmark (1982-88)	3b	Cohort R	104	40	≥5 drinks/day vs 3-4 drinks/day, ≤2 drinks/day, previous abuse	Yes	Evacuation of subdural haematoma	Mortality Morbidity	Chi^2 test	No	35% mortality vs 11% ($p<0.05$), 65% compl vs 37% ($p<0.01$)	3.1 (1.2-7.9)	4.2 (1.2-14.2)	———

P: Prospective studies. R: Retrospective studies. RCT: Randomised clinical trial.

Table B in the appendix. *Studies of the biological alcohol marker CDT in somatic hospital paitents. [The numbers in brackets were calculated by the author].*

General surgery	Country Study year	Evidence	Design*	Total no pts.	No alc pts.	Definition alc. abuse	Inclusion criteria	Sampling time	Analysis	Cut-off value	Corr. coef.	Sensitivity	Specificity	Positive pred. value	Negative pred. value
Bean (1995)	USA (Unknown)	4	Cases	15	0	≥60 g alc/day	Cirrhotic w	Unknown	CDTect RIA	25 U/l w	———	———	60%	———	———
Bell (1993)	Norway (Unknown)	3	Case-Control	420	102	>50 g alc./day	Liver diseases	Unknown	CDTect RIA	27 U/l w 20 U/l men	———	61%	92%	———	———
Bell (1994)	Norway (Unknown)	2	Cohort	502	26	>50 g alc./day	Medical diseases	Day after admission	CDTect RIA	28 U/l w 20 U/l men	Unknown	69%	92%	39%	98%
Bråthen (2000)	Norway (1995-1996)	2	Cohort	158	53	AUDIT pos (≥8 in score)	Neurological diseases	On admission	%CDT kit	5.0%	0.27	41%	84%	56%	74%
Bråthen (2001)	Norway (Unknown)	2	Cohort	484	40	>40 g w >60 g men	Neurological diseases	Unknown	a) CDTect RIA b) % CDT	a) 26 & 20 U/l b) >6.0%	Unknown	a) 61% b) 40%	a) 88% b) 93%	a) 31% b) 34%	a) 96% b) 94%
Jaakkola (1994)	Finland (Unknown)	3	Cohort	86	42	>80 g alc./day	Acute pancreatitis	Day of admission	CDTect RIA	17 U/l	0.46	75%	100%	100%	77%
Lesch (1996)	Austria (Unknown)	2	Cohort	101	21	>60 g alc./day	Surgical and medical pts	Day of admission	%CDT kit	2.4%	Unknown	70%	98%	94%	93%
Meregalli (1995)	Italy (1992-1993)	3	Case-Control	191	68	≥60 g alc./day	Medical diseases	Unknown	CDTect RIA	26 U/l w 20 U/l men	———	67%	82%	———	———
Mundle (1999)	Germany (Unknown)	4	Cases	177	a) ≤4d abst b) >4d abst	≥60 g alc./day	Alcohol dependence	Day of admission	%CDT kit	>2.0%	———	a) 56% b) 14%	———	———	———
Nalpas (1997)	France (Unknown)	3	Case-Control	346	195	Unknown	Liver diseases	Unknown (retrospective)	CDTect RIA	27 U/l w 20 U/l men	———	56% w 72% men	75% w 74% men	———	———
Reynaud (2000)	France (Unknown)	3	Case-Control	268	a) 84 abus b) 82 dep	DSM-IV and >20 g alc./day	Emergency patients	Unknown	CDTmaec-td	60 mg/l	———	a) 67% b) 85%	a) 97% b) 97%	a) 95% b) 96%	a) 79% b) 89%
Reynaud (2001)	France (1997-1998)	4	Cases	166	166	DSM-IV	Acute intox. BAL >0.8 g/l	On admission	CDTmaec-td	60 mg/l	———	80%	———	———	———
Schröder (1998)	Germany (1994-1996)	2	Cohort	46	33	≥75 g alc./day	Surgical pts (oesoph res)	Preoperative	CDTect RIA	Unknown	Unknown	71%	84%	92%	55%
Sharpe (1996)	Ireland (Unknown)	3	Case-Control	125	38	≥40 g alc./day	Medical diseases	Day after admission	CDTect RIA	12 U/l		71%	63%	[46%]	[83%]
Sillinaukee (2001)	Germany, France, Japan, Spain, Finland	3	Case-Control	1412	472	>60 g alc./day	Pts, staff, stud, donors	Unknown	CDTect RIA	26 U/l w 20 U/l men	———	40% w 58% men	94% w 94% men	———	———
Sorvajärvi (1996)	Finland	3	Case-Control	172	83	>80 g alc./day	Patients and staff	Unknown	a) CDTect RIA b) % CDT kit	a) 26 & 20 U/l b) >2.5%	Unknown	a) 59% b) 34%	a) 81% b) 100%	———	———
Spies (1995b)	Germany (Unknown)	2	Cohort	105	69	≥60 g alc./day	Trauma patients	On admission before infusion	a) CDTect RIA b) % CDTmaec-td	a) 26 & 20 U/l b) 9 mg/ml	Unknown	a) 74% b) 83%	a) 95% b) 100%	a) 94% b) 100%	a) 69% b) 73%
Spies (1996)	Germany (Unknown)	2	Cohort	213	121	≥60 g alc./day	Surgical patients	Preoperatively before infusion	CDTmaec-td	9 mg/l	Unknown	58%	90%	Unknown	Unknown
Stauber (1995)	Austria (Unknown)	3	Cohort	106	17	≥60 g alc./day	Susp liver diseases	Unknown	CDTect RIA	26 U/l w 20 U/l men	Unknown	59%	85%	43%	92%
Stibler (1987)	Sweden (Unknown)	2	Cohort	102	15	≥60 g alc./day	Susp liver diseases	Unknown	CDTect RIAw	74 mg/l	0.67	87%	100%	100%	98%
Tønnesen (1999a)	Denmark (1996)	2	Cohort	538	38	≥60 g alc./day	Surgical patients	On admission before infusion	CDTect EIA	26 U/l w 20 U/l men	0.58 l w 0.77 men	80% w 100% men	96% w 97% men	44% w 82% men	99% w 97% men
Yersinm (1995)	Switzerland (1992)	3	Case-Control	455*	85	>40 g w >60 g men	Medical diseases	Unknown	CDTect EIA	26 U/l w 20 men	[0.20 w] [0.25 men]	——— 58% men	——— 82% men	——— [51% men]	——— [93% men]

*) 199 CAGE pos. + 256 CAGE neg. w = women

Table C in the appendix. *Incidence of significant bacteriuria pre- and postoperatively in alcohol and control group undergoing transurethral prostatectomy (basic data from Tønnesen 1988).*

Species	Preoperatively		Postoperatively		1 month postoperatively	
	alcohol	control	alcohol	control	alcohol	control
Escherichia coli	3	0	8	1	2	1
Klebsiella pneumoniae	2	0	8	2	1	1
Streptococcus faecalis	1	0	4	3	2	1
Staphylococcus aureus	1	0	4	0	1	1
Coagulase negative staphylococci	0	0	3	2	1	0
Enterobacter cloacae	1	0	2	1	0	0
Proteus mirabilis	0	0	2	2	1	0
Beta-haemolytic streptococci B	0	0	0	0	1	1
Diphtheroid corynebacteriae	0	0	1	0	0	0
Total	8	0	32	11	9	5
Number of patients requiring treatment *	4 (5%)	0 (0%)	29 (39%)	10 (13%) **	7 (7%)	2 (3%)
Number of patients with polymicrobial growth	2	0	3	1	2	2

*) Patients with urinary catheter did not always need treatment.
**) $p \leq 0.01$