Acute and chronic pancreatitis: epidemiology and clinical aspects
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Citation for published version (APA):
Acute pancreatitis and concomitant use of pancreatitis-associated drugs

ACCEPTED AM J GASTROENTEROL 2011

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Abstract

BACKGROUND Drug-induced pancreatitis (DIP) is considered a relative rare disease entity, perhaps due to lack of recognition. We evaluated the prevalence of pancreatitis-associated drugs in a Dutch cohort of patients admitted for acute pancreatitis and identified the proportion acute pancreatitis possibly attributable to the use of drugs.

METHODS Multi-center observational study (EARL study). Aetiology, disease course, use of pancreatitis-associated drugs at hospital admittance and discontinuation of these drugs were evaluated. Drugs were scored by means of an evidence-based DIP classification system.

RESULTS The first documented hospital admissions of 168 patients were analyzed. Seventy out of 168 (41.6%; 95% CI: 34.5-49.2) patients used pancreatitis-associated drugs at admission. In 26.2% (44/168; 95% CI: 20.1-33.3) of cases at least one class I pancreatitis-associated drug was used. Possibly DIP was present in 12.5% (21/168; 95% CI: 8.3-18.4); in less than half of these patients (9/21 or 42.9%; 95% CI: 24.5-63.5) the prescribed drugs were actually discontinued, with no recurrence of acute pancreatitis later on. Among the remaining 12 patients without discontinuation of their drugs use and in absence of an alternative etiologic cause of acute pancreatitis, 8 patients used a class I pancreatitis-associated drug, representing 4.8% (8/168, 95% CI: 2.4-9.1) of the total study population.

CONCLUSIONS In this series a remarkably high percentage of patients who were admitted because of an attack of acute pancreatitis used pancreatitis-associated drugs. Physicians should be more aware of the possibility of DIP in patients with otherwise unexplained acute pancreatitis and act appropriately by discontinuation of the drug.
Introduction

Drugs are considered a relatively rare cause of acute pancreatitis (AP). The true incidence of drug-induced pancreatitis (DIP) is not accurately known and estimated between 0.1% and 2% of all cases with AP.\(^1\)\(^-\)\(^7\) The diagnosis of DIP is often challenging because DIP has no unique clinical features that distinguishes it from AP due to other causes. Evidence linking drugs to AP is mostly derived from case reports and case-control studies. Generally, evidence is assessed based on criteria such as reasonable temporal sequence from drug administration to the development of AP, exclusion of other causes, and a positive re-challenge with the drug. In the last decades several drug classification systems of DIP have been published. In 1980, Mallory and Kern proposed a system in which a drug was classified as having either a definite, probable or possible association with AP.\(^8\) Ever since, several review articles have used this, sometimes adapted or modified, ‘three group’ classification system. In 2007, Badalov et al. published the latest adapted classification system. They categorized 120 drugs in four classes based on the published weight of evidence with AP [Table 1].\(^9\) Class I includes drugs of which at least one case report with recurrence of AP after rechallenge has been published. Class I drugs are subdivided into class Ia and Ib, depending on whether or not other potential causes have been ruled out. Class II includes drugs in which there is a consistent latency in 75% or more of the reported cases. Class III includes drugs that have neither a rechallenge nor a consistent latency period, but at least two cases are reported. Class IV drugs are similar to class III, but only one case report is reported.

### Table 1  Classification system of drug-induced acute pancreatitis according to Badalov et al.\(^9\)

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
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<tbody>
<tr>
<td>Class Ia drugs</td>
<td>At least 1 case report with positive rechallenge, excluding all other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs</td>
</tr>
<tr>
<td>Class Ib drugs</td>
<td>At least 1 case report with positive rechallenge; however, other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs were not ruled out</td>
</tr>
<tr>
<td>Class II drugs</td>
<td>At least 4 cases in the literature, Consistent latency (≥75% of cases)</td>
</tr>
<tr>
<td>Class III drugs</td>
<td>At least 2 cases in the literature, No consistent latency among cases, No rechallange</td>
</tr>
<tr>
<td>Class IV drugs</td>
<td>Drugs not fitting into the earlier-described classes, single case report published in the medical literature, without rechallenge</td>
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We evaluated the aetiology, disease course, use and discontinuation of pancreatitis-associated drugs at hospital admittance and discharge in a convenient cohort of patients with an established clinical diagnosis of AP or recurrent AP, according to the latest evidence-based DIP classification system.

Methods

Study population
In August 2003 an observational prospective multicenter (2 academic and 16 community hospitals) cohort study in the province of Northern Holland was initiated (the EARL study). Patients with AP, recurrent AP and/or CP who were admitted to the hospital or attended the out-patient clinic, were asked to participate. Patient inclusion ended in May 2006. A total of 512 patients were entered in the study database. For the present analysis, follow-up data until the end of October 2007 were used. Hence, patients were monitored for a minimum of 17 and maximum of 50 months. Approximately two thirds of patients had AP or recurrent AP and the remaining patients suffered from CP. Diagnosis and treatment of AP were decided upon by the attending physician(s) of each participating hospital.

For the present study, we included those patients with a confirmed diagnosis of AP or recurrent AP, of whom at least one fully documented hospital admission during the study period was available. The first documented hospital admission of each patient was considered. If the patient had a recurrent attack in the observation period and used pancreatitis-associated drugs at first admission, then the subsequent admissions were also analyzed. AP was defined as a clinical disease entity with acute epigastric pain combined with a serum amylase and/or lipase value of more than three times the upper limit of normal, and in the absence of any feature of CP. Disease severity (mild and severe AP) was defined according to the Atlanta criteria. Recurrent AP was defined as more than one attack of AP in the time period before inclusion and/or during the observation period.

Hospital records and nursing reports were thoroughly reviewed. Furthermore, study questionnaires with e.g. items about drugs use were collected and analysed once a year. The study items were recorded in a study database. The following information was retrieved from the database: demographic data, etiological factors, drug use at hospital admission and at discharge, and severity of the attack.

The aetiology was assessed after a review of hospital and out-patient charts. This included reported alcohol consumption (retrieved from hospital charts and study questionnaires), family history of pancreatic disease, laboratory results (e.g. liver function tests, triglycerides, calcium) and imaging procedures (e.g. ultrasound, CT, MRCP, ERCP and EUS). However, genetic disorders, such as mutations in cationic trypsinogen,
SPINK-1 and CFTR gene were not ruled out. In addition, all registered drugs used at hospital admission were classified as pancreatitis-associated or not and subsequently categorized in one of four classes according to the DIP classification system of Badalov et al.9 New onset use of diclofenac (a class IV drug) just before hospital admission was discarded and not classified as pancreatitis-associated because this drug was most likely prescribed to manage pain associated with the attack of AP or gallstone colick. ‘Possibly DIP’ was defined as an attack of AP in the absence of other etiological factors besides the use of pancreatitis-associated drugs at admission. When the prescription of pancreatitis-associated drugs had been discontinued and no recurrence of AP developed hereafter, it was assumed that the treating physician had indeed identified the incidence of AP as drug-induced.

If the diagnostic work-up was complete (e.g. without genetic testing) and did not identify any known etiological cause the patient was classified as suffering from idiopathic AP. For example, microlithiasis had to be ruled by the use of at least one of the following examinations: EUS, ERCP or MRCP. However, if the diagnostic work-up was incomplete (e.g. microlithiasis or pancreatic divisum not ruled out) the patient was classified as having indefinite AP.

The study protocol was approved by all local ethics committees and informed consent was obtained from all patients.

Statistical analysis
In this observational study descriptive statistics were used. Categorical data were reported as proportions along with Wilson’s 95% confidence intervals (95% CI). Fisher’s exact test was used to compare the aetiology of AP patients using pancreatitis-associated drugs at admission against the ones who did not. A p-value less than 0.05 indicated statistical significance. All statistical analyses were performed using The Statistical Package for the Social Sciences (SPSS) version 15.0 (SPSS, Chicago, IL) and Computer Programs for Epidemiologists (PEPI) version 4.0 (Sagebrush Press, Salt lake City, 2001).

Results
Aetiology and disease course of study population
From the original EARL pancreatitis study database, a total of 198 hospital admissions with AP or recurrent AP were identified with a fully documented admission record. Twenty one patients had more than one documented hospital admission during the study period. As previously mentioned, the first documented hospital admission of each patient was considered for the present analysis. Ultimately, 168 patients with a completed review of a hospital admission were analyzed. In 29.2% (49/168; 95% CI:22.8-36.4) of patients a CT scan was performed within the first four days after admission
which confirmed in all patients the diagnosis of AP. The baseline characteristics of the study population are presented in Table 2. Male and female patients were equally represented and the median age was 50 years (range 18-95). One quarter of patients suffered from recurrent attacks of AP.

The most common etiological factors were biliary stones/sludge (71/168, 42.2%; 95% CI: 35-49.8) followed by alcohol abuse (32/168, 19%; 95% CI: 13.8-25.7) and post-ERCP (19/168, 11.3%; 95% CI:7-17) \[table 2\]. Three patients had a combination of etiological factors. One patient classified as having a biliary cause also suffered from hypercalcaemia and two patients with alcohol abuse suffered also from hyperlipidaemia. In 23.8% (40/168; 95% CI: 18.0%-30.8) the cause of AP was unknown (idiopathic or indefinite AP) or possibly drug-related.

Overall, in 89.3% (150/168; 95% CI: 83.7-93.1) of cases the disease course was mild. In case of a severe course the leading local complication was pancreatic or peripancreatic necrosis. Out of these 11 patients, only three also developed organ failure.

**Pancreatitis-associated drugs and disease course**

[Table 3] also shows the prevalence of patients using pancreatitis-associated drugs. At admission 70 patients (41.6%; 95% CI: 34.5-49.2) were using these drugs, excluding the 7 patients (5 of whom had a gallstone related AP) who only used diclofenac at the time of admission (see Methods section). Among the 70 patients, a biliary cause of AP was found in 30 (42.9%; 95% CI: 31.9-54.5), alcoholic aetiology was identified in 12 (17.1%; 95% CI: 10.1-27.6), post-ERCP in 6 (8.6%; 95% CI: 4-17.5) and other causes in 1 (1.4%; 95% CI: 0.3-7.7). In 21 patients (30%; 95% CI: 20.5-41.5) the cause was unknown (idiopathic or indefi-
nite or possibly drug-related. The distribution of known etiologic factors other than drugs in patients using pancreatitis-associated drugs did not differ from the distribution in patients who did not use pancreatitis-associated drugs (Fisher’s exact; p=0.63).

Looking more closely into the intensity and type of pancreatitis-associated drug use [table 4], we found that 45 patients (64.3%; 95% CI: 52.6-74.5) used a single pancreatitis-associated drug, 17 patients (24.3%; 95% CI: 15.8-35.5) used a combination of two drugs, 5 (7.1%; 95% CI: 3.1-15.7) a triple combination, and 3 (4.3%; 95% CI: 1.5-11.9) a quadruple combination. Almost two-thirds of all patients with pancreatitis-associated drugs at admission, 44/70 (62.9%; 95% CI: 51.1-73.2), used at least a class I drug, predominantly class Ia (28/44 or 63.6%; 95% CI: 48.9-76.2). Most often, the class I drug was a cardiovascular or gastrointestinal agent. The most frequently used class I drugs, single or in combination with other drugs, were simvastatin (class Ia) 29.5% (13/44; 95% CI: 18.2-44.2), enalapril (class Ia) 22.7% (10/44; 95% CI: 12.8-37) and omeprazole (class Ib) 20.5% (9/44; 95% CI: 11.2-34.5).

### Table 3 Frequency of etiological factors of the different study populations

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Total study population (n=168)</th>
<th>No pancreatitis-associated drugs (n=98)</th>
<th>Pancreatitis-associated drugs (n=70)</th>
<th>Class I pancreatitis-associated drugs (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary</td>
<td>71</td>
<td>41</td>
<td>30</td>
<td>17</td>
</tr>
<tr>
<td>Alcohol</td>
<td>32</td>
<td>20</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Post-ERCP</td>
<td>19</td>
<td>13</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>5</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Unknown or (possibly) DIP</td>
<td>40</td>
<td>19</td>
<td>21</td>
<td>16</td>
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### Table 4 Use of pancreatitis-associated drugs (n=70)

<table>
<thead>
<tr>
<th>Number of associated drugs</th>
<th>Highest class of associated drugs</th>
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<td>4</td>
<td>2</td>
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<tr>
<td>Total</td>
<td>28</td>
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In 84.3% (59/70; 95% CI: 74-91) of all patients who used pancreatitis-associated drugs the disease course was mild; in patients who used at least one class Ia or class Ib drug, similar observations were made, respectively 82.1% (23/28; 95% CI: 64.4-92.1) and 93.8% (15/16; 95% CI: 71.7-98.9).

Possibly drug-induced pancreatitis and disease course
As demonstrated in Table 3, 21 out of 168 patients (12.5%; 95% CI: 8.3-18.4) used pancreatitis-associated drugs in absence of another etiologic cause and the incidence of their AP attack might thus be drug-induced.

In less than half of them (9/21 or 42.9%; 95% CI: 24.5-63.5), the prescription of pancreatitis-associated drugs was discontinued and no recurrence of AP developed later on, suggesting that the treating physician justifiably had identified their AP as drug-induced or DIP. Thus the prevalence of DIP is 5.4% (9/168; 95% CI: 2.8-9.9). These patients had been prescribed: azathioprine (class Ib) (n=2); azathioprine together with prednisone (class III) (n=1); prednisone and sulfasalazin (not classified) (n=1); pravastatin (class Ia) (n=1); pravastatin together with lamivudine (class Ib), DDI (class II) and ritinovir (class IV) (n=1); enalapril (class Ia) (n=1); enalapril together with furosemide (class Ia) (n=1); and, finally, omeprazol (class Ib) together with atorvastin (class III) and fosinopril (not classified) (n=1).

In the remaining 12 patients (57.1%; 95% CI: 36.5-75.5) on pancreatitis-associated drugs, their prescription was not discontinued at admission or discharge, despite the absence of other risk factors (10 idiopathic and 2 indefinite AP). These patients had been prescribed: simvastatin (class Ia), enalapril (class Ia), metformin (class III) and prednissone (class III) (n=1); simvastatin (n=2); simvastatin together with hydrochlorothiazide (class III) (n=1); enalapril (n=2); losartan (class Ib), omeprazole (class Ib) and hydrochlorothiazide (n=1); omeprazole, prednisone and alendronate (class III) (n=1); carbamazepine (class III) and clarithromycin (class III) (n=1); estrogen (class II) (n=1); cimetidine (class III) (n=1); and, finally, gemfibrozil (class IV) (n=1). Hence, 8 patients used a class I drug (either or not in combination) without its discontinuation in absence of another etiologic factor of AP (6 idiopathic and 2 indefinite AP). Their AP attack probably went unrecognized as drug-induced. These 8 patients constituted 4.8% (8/168; 95% CI: 2.4-9.1) of our study population.

In all 9 patients with a recognized DIP the disease course was mild. Out of the other 12 patients the disease course was mild in 83.3% (10/12; 95% CI: 55.2-95.3).

Recurrent AP and pancreatitis-associated drugs
Eighteen out of the 70 patients who used pancreatitis-associated drugs suffered from recurrent AP. Ten patients with a recurrent AP had their first attack before the study period and detailed information about the use of pancreatitis-associated drugs at the time of the previous admission was lacking. For one patient, detailed information of
the second admission in the observation period was unavailable. Of the remaining 7 patients, 5 were still using their pancreatitis-associated drugs at the time of admission for a recurrent attack. Four out of these five patients were still using at least one class I drug: omeprazole (class Ib) (n=2); omeprazole together with losartan (class Ib) and hydrochlorothiazide (class III) (n=1); simvastatin (class Ia) together with hydrochlorothiazide (n=1); and rantidine (class III) (n=1). Only the patient using simvastatin/ hydrochlorothiazide was classified as AP from unknown aetiology (idiopathic AP). The others were classified as biliary or alcoholic AP. In 88.9% (16/18; 95%CI: 67.2-96.9) of cases with a recurrent AP the disease course was mild.

**Discussion**

The present paper reports an observational study in which the prevalence of pancreatitis-associated drug use at hospital admission for AP is assessed in a Dutch multi-center setting according to the latest evidence-based DIP classification system. Over the last decades the classification systems of DIP were subject to different viewpoints and frequently adapted. In 1980, Mallory and Kern proposed a system in which a drug was classified as having either a definite, probable or possible association with pancreatitis based on multiple criteria.8 Ever since, several review articles have used this ‘three group’ classification system.3-11-13 In 2005, Trivedi et al. revised this ‘three group’ classification system putting more weight on the number of reported cases and a positive re-challenge.14 In the present study we used the latest evidence-based DIP classification system as published by Badalov et al. in which the number of reports are less important and more weight is given to a positive re-challenge, the exclusion of other causes, and the time relation between drug use and the onset of AP.9 We show that pancreatitis-associated drugs are very frequently (70/168 or 41.6%) used at the time of hospital admission for

**Table 4 Use of pancreatitis-associated drugs (n=70)**

<table>
<thead>
<tr>
<th>Number of associated drugs</th>
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<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
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</table>
(recurrant) AP. In more than a quarter of cases (44/168 or 26.2%), these pancreatitis-associated drugs are ranked as class I drugs, the highest level of evidence for an association with AP. This percentages are even higher compared to the results of a former pilot study done by our study group, when 16 out of 60 (27%) patients admitted for AP used pancreatitis-associated with DIP. 5 out of 60 (8.3%) used definite pancreatitis-associated drugs. However, the DIP classification system used in that pilot study differed from the present study.

The question at hand is whether this high percentage is merely a reflection of the general use of pancreatitis-associated drugs in the Dutch population and, more specifically, in the population at risk to develop AP, or whether this is a true indication of a causal relationship between the use of these drugs and the development of AP. Badalov et al. use a latency period between initiating a drug and the development of AP as a criterion for the class II drugs. However, we do not have valid information about how long patients were taking the pancreatitis-associated drugs. To prevent overestimation of the use of pancreatitis-associated drugs at forehand, we did not count the use of diclofenac as pancreatitis associated, because its use is most probably related to short term use prior to the hospital admission to treat pain associated with the attack of AP or colic induced by gallstones. A causal relationship of the use of estrogens/oral contraceptives and the development of AP in our study is doubtful. In the DIP classification system estrogens are categorized as class II drugs. However, out of the five females who used oral contraceptives, none had hyperlipidaemia at admission which is thought to be the trigger for the development of AP. Only one woman had an AP of unknown aetiology (idiopathic AP).

Furthermore, the majority of the class I pancreatitis associated drugs registered in this study are cardiovascular or gastrointestinal drugs, which belong to the classes of drugs that are most commonly used in the general population. For example, two of the most prevalent class I drugs which were encountered in the present study are simvastatin (HMG-CoA reductase inhibitor) and omeprazole (PPI) which rank in the top ten of most prescribed drugs in the Netherlands (www.sfk.nl).

Whether these types of drugs are more commonly used in AP patients is not known. However, a recent cohort study from the United Kingdom showed that patients with type 2 diabetes mellitus have a higher risk for the development of AP. In this study it was demonstrated that smoking and alcohol use, among other factors, were significant predictors of AP, but after adjusting for these factors the risk of developing AP remained elevated. Generally, cardiovascular disease is a main complication of diabetes and of smoking. It is imaginable that a proportion of AP patients are more frequent users of antihypertensive and cholesterol lowering agents and hence run a proportionally greater risk of developing DIP. A intriguing and unresolved issue is how these drugs actually promote the development of AP. For some drugs there are suggested, but unproven, mechanisms of action for the development of DIP including cytotoxic and
metabolic effects, accumulation of toxic metabolites, constriction of the sphincter of Oddi, and hypersensitivity reactions. It should be realized however that the underlying condition for which the drug is taken may act as a confounding factor and is the factual cause for the risk increase. Another likely possibility is that in cases with concomitant risk factors certain drugs may act as a co-factor or disease modifier. These drugs would then lower the 'threshold' for the developing pancreatic inflammation and in combination with e.g. alcohol triggering the cascade for the final progression into AP. Whether this concept holds true in clinical practice needs to be further studied, for example in experimental animal studies.

The observation that in almost one out of 20 patients the class I drug(s) was not stopped in case of an attack of AP of unknown aetiology, is striking. Of course this is an observational study and it is not definitely known whether continuation of such drug in certain cases was deliberate. In the medical charts however we found no proof of this, e.g. that continuation was required because of an underlying disease while no alternative medication was available. Therefore, it is not more than logical to contemplate that the drug was simply not recognized as a drug associated with DIP.

At the same time however, it should be stated that in 7 patients on pancreatitis-associated drugs in whom an etiologic factor was identified other than pancreatitis-associated drugs, the drug(s) was nevertheless stopped at discharge; three of them used at least one class I drug (results not reported). In these cases the attending physician in all probability valued the drug as a co-factor.

We found that possible DIP was present in 12.5% of the patients with an incidence of AP and that it seemed recognized as DIP by the treating physician in almost half of these cases (5.4%). Even if we consider the latter percentage as the lower limit of the prevalence of DIP, it still is considerably higher than generally in the literature reported outcomes ranging between 0.1% and 2%. However, recently also Vinklerová et al. concluded from there single center retrospective analysis that in 5.3% (9/170) the AP was drug-induced. Mennencier et al. report from there retrospective analysis an even higher percentage of 8.3% (9/108). Of note, in 8 out of the 9 DIP cases at least one class I drug was used and that after cessation of the drugs no pancreatitis recurrence occurred with the recognition that in selected cases the follow-up period may have been too short. In concurrence with other literature reports the disease course was in all cases mild.

In conclusion, the prevalence of pancreatitis-associated drugs in this cohort of Dutch patients admitted for an attack of acute (recurrent) pancreatitis was remarkably high. One out of twenty AP patients used at least one pancreatitis-associated class I drug and these drugs were not discontinued at hospital admission in the absence of an alternative etiologic explanation. Physicians must be more aware of the possibility of DIP and discontinue pancreatitis-associated drugs at admission accordingly, in particular in recurrent AP of unknown cause. Larger epidemiological studies are warranted to
establish the true risk of AP for various drugs using a uniform and widely accepted DIP classification system.\textsuperscript{20, 23}

Acknowledgements

The authors thank all the members of the ‘Amsterdam Gastroenterological Society’ for their support, contribution and inclusion of patients in the EARL study.
Appendix

Other members of the EARL study group:

A.A. van Bodegraven, VU University Medical Center, Amsterdam, Amsterdam; I.C.E. Wesdorp, Sint Lucas/Andreas Hospital, Amsterdam; H.A. van Heukelem, Slotervaart Hospital, Amsterdam; A.A. Geraerdts, Onze Lieve Vrouwe Gasthuis, Amsterdam; A. Teunen, Boven IJ Hospital, Amsterdam; L.A. Noach, Amsteland Hospital, Amstelveen; W. Bruins Slot, Spaarne Hospital, Hoofddorp; G.H. de Groot, Red Cross Hospital, Beverwijk; R.J.L.F. Loffeld, Zaans Medical Center, Zaandam; P.P. Viergever, Gemini Hospital, Den Helder; M. Klemt, Westfries Gasthuis, Hoorn; P.R. Oosting, Waterland Hospital, Purmerend; M.J. Wagtmans, Flevo Hospital, Almere; P.J. Kingma, Tergooiziekenhuizen, location Blaricum; C.Y. Ponsioen, Tergooiziekenhuizen, location Hilversum
References