Long-term clinical outcome for patients poisoned by the fungal nephrotoxin orellanine

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Abstract

Background: Accidental intake of mushrooms of the Cortinarius species (deadly webcap) may cause irreversible renal damage and the need for dialysis or transplantation. The species is found in forests of Northern Europe, Scandinavia and North America and may be mistaken for other edible mushrooms. The highly selective nephrotoxic compound of the mushroom is called orellanine. Very little is known about the long-term effects of the nephrotoxin.

Methods: We identified patients who ingested deadly webcap in the period of 1979 to 2012. Informed consent and medical records were obtained for 28 of the 39 cases that occurred during the 34-year period. A case control group was also studied based on sex, age and initiation of dialysis or transplantation.

Results: The average age at time of the accidental intake was 40 ± 3 years (n = 28). 64% of patients were male, and 22 of 28 patients developed acute kidney injury requiring dialysis. Serum creatinine peaked at 1 329 ± 133 μmol/l, and serum urea was 31 ± 3.5 mmol/l. No signs of acute damage were present in any other organ. The average time of follow-up was 16.9 ± 2.1 years (1.24–34.3 years, n = 28). 15 patients were transplanted and 3 also had a second graft. At follow-up, 23 patients were alive, and five had died at ages of 67 ± 5 (range 54–84). The outcome was similar in the case control group with 6 deaths in 20 patients.

Conclusion: We conclude that the long-term prognosis for patients poisoned by deadly webcap who lost their renal function is not different compared to other patients in active uremic care.
Suggested therapies during the years have been hemodialysis, hemoperfusion, corticosteroids and antioxidant therapies with highly varying and inconclusive results [4, 20, 21]. Regarding long-term effects of the intoxication, there are only a few reports following transplantation [17, 22]. There are no long-term follow up on patients after the initial acute kidney injury phase. Therefore, we tried to identify all cases of deadly webcap intoxication during the last three decades in the most affected (South-Western) region of Sweden and compared their outcome with a case-control group of patients. Our hypothesis was that the poison might have long-term effects or increase patient morbidity and mortality. Hence, a long time follow up of a patient cohort would be of interest.

Methods
Study population
We included all patients accidentally poisoned by intake of the mushroom deadly webcap (or *Cortinarius rubellus*, also known as *Cortinarius speciosissimus*) admitted to any of the hospitals in the Western part of Sweden during the period of January 1979 to December 2012. The total number of patients was 39. In this report, 28 patients were included based on informed consent and available medical records, see Table 1 for demographic data.

Case control population
For each patient included in the study population that developed CKD5 (chronic kidney disease stage 5), we randomly included another patient as case control from the dialysis unit and another from the transplantation centre at Sahlgrenska University Hospital. Patients with diabetes or other systemic disease were excluded. The case controls were matched in age, sex, comorbidity and the year of the initiation of dialysis or transplantation. Such case control subjects could be found for all study patients in the dialysis group. However, three case controls are missing during certain years for the transplantation group due to large age differences. Most of the case control patients included had interstitial nephritis (75%), glomerulonephritis, or polycystic kidney disease, see Table 3 for demographic data.

Kidney morphology
Kidney biopsies were taken using gauge 16 needles, fixed in buffered paraformaldehyde, embedded in paraffin, sectioned and stained with standard dyes (haematoxylin-eosin, trichrome, silver and periodic acid-Schiff) and evaluated by a renal pathologist.

Statistical analysis
Results are presented as mean ± SEM (standard error of the mean). Differences between groups were calculated using the Gehan-Breslow-Wilcoxon test.

Results
Study population
Of the 39 patients identified, we were able to include 28 patients in the study. This was mainly due to difficulties to be able to get in contact and obtain an informed consent form from all patients.

Of the 28 patients, 22 required dialysis initially, and 6 did not, Table 1. After 1 month, 21 patients had CKD5 requiring dialysis or transplantation and 7 patients had CKD stage 3. Thus, there was a 4.5% chance for a patient initially requiring dialysis to regain renal function during the first month after the intoxication (1/22). Of the 7 patients that were dialysis-free 1 month after the intoxication, all regained most of their renal function within the first year reaching CKD stage 1 or 2.
| No. | Biopsy (Y/N) | 1st trpl Year | 2nd trpl Year | Initial dialysis | Cont on dialysis | GFR Year | GFR | Age at intox | Admission Year | BP | Hb | Alb | Crea | Alat | Alp | Bil | Urea | Asat | Cancer after intox |
|-----|--------------|---------------|---------------|-----------------|-----------------|-----------|-----|-------------|----------------|-----|-----|-----|------|------|-----|-----|------|-----|------------------|
| 1a  | N            | N Y N N       | 47            | 1979            | 130/70          | 116       | 39  | 889         | 0.22           | 36  | 5   | 9   | N    | N    | N   | N   | N    | N   | N                |
| 2a  | N            | N Y N N       | 24            | 1979            | 140/80          | 149       | 71  | 600         | 0.19           | 0.29 | N   | 0.33|
| 3   | N 1980       | N Y N Y       | 35 1115       | 2011            | 185/100         | 124       | 150 | 37          | 0.3            | 3   | 4   | 3   | Yb   | Yb   | Yb  | Yb  | Yb   | Yb  | Yb               |
| 4   | N 1986       | Y N N Y       | 55 2012       | 1985            | 170/110         | 95        | 71  | 542         | 0.54           | 4.1  | 7.5 | 23  | 0.52 |
| 5   | Y N N N      | 26            | 1985          | 120/80          | 86              | 1270      | 0.3 | 3           | 37  | 7   | 17  | 0.3  | N    | N    | N    | N    | N    | N                |
| 6a  | N 1987       | 38 2004       | 21            | 1985            | 130/80          | 101       | 1800| 24          | 0.7            | 0.22 | 0.33|
| 7   | Y 1988       | N Y N Y       | 107 2009      | 1987            | 130/80          | 101       | 1800| 24          | 0.7            | 0.22 | 0.33|
| 8   | N 2012       | N N N N       | 40            | 1987            | 130/80          | 144       | 126 | 0.7         | 2.2            | 11   | 0.47|
| 9a  | N            | Y Y Y         | 26            | 1990            |                 |           |     |             |                 |     |     |     | Yb   | Yb   | Yb  | Yb  | Yb   | Yb  | Yb               |
| 10  | N            | Y Y Y         | 16            | 1990            |                 |           |     |             |                 |     |     |     | Yb   | Yb   | Yb  | Yb  | Yb   | Yb  | Yb               |
| 11  | N 1992       | 39 1991       | N Y           | 1991            | 130/70          | 73        | 123 | 1133        | 0.47           | 3    | 7.4 | 45  | 0.23 |
| 12  | N            | Y Y Y         | 41            | 1991            | 130/80          | 119       | 32  | 1074        | 0.19           | 3.3  | 7.9 | 34  | 0.17 |
| 13  | N 1992       | Y Y Y         | 21            | 1991            | 135/80          | 125       | 45  | 675         | 0.41           | 2.7  | 7.5 | 42  | 0.34 |
| 14  | N 1999       | 41 1979       | Y Y           | 160/90          | 143             | 41         | 1630| 6           | 160/90         | 143  | 41  | 1630|
| 15  | N 2000       | Y Y Y         | 68            | 1984            | 180/95          | 125       | 72  | 970         | 0.3            | 3    | 7   | 0.3 |
| 16  | N 2000       | Y N Y         | 28            | 2008            | 130/70          | 123       | 32  | 1333        | 0.47           | 3    | 7.4 | 45  | 0.23 |
| 17  | N 2001       | Y N Y         | 52            | 2002            | 130/70          | 123       | 32  | 1333        | 0.47           | 3    | 7.4 | 45  | 0.23 |
| 18  | N 2002       | Y N Y         | 44            | 2012            | 130/70          | 123       | 32  | 1333        | 0.47           | 3    | 7.4 | 45  | 0.23 |
| 19  | N 1995       | Y Y Y         | 40            | 1984            | 180/100         | 111       | 69  | 970         | 0.26           | 2.2  | 14  | 10  | 0.31 |
| 20  | Y 2007       | Y Y Y         | 46            | 1999            |                 |           |     |             |                 |     |     |     | Yb   | Yb   | Yb  | Yb  | Yb   | Yb  | Yb               |
| 21  | N 2013       | Y N Y         | 48            | 2007            | 129/71          | 1052      | 0.28| 0.14        | 2.2            | 6.4  | 27.6| 0.3 |
| 22  | N 2009       | Y N Y         | 40            | 2009            | 129/71          | 174/97    |     |             |                 |     |     |     | Yb   | Yb   | Yb  | Yb  | Yb   | Yb  | Yb               |
| 23a | N N N N      | 25            | 2010          | 160/104         | 115             | 243       | 0.45| 1.1         | 6              |     |     |     | Yb   | Yb   | Yb  | Yb  | Yb   | Yb  | Yb               |
| 24  | Y 2012       | Y N Y 11      | 12 2012       | 125/87          | 127             | 37         | 2809| 0.12        | 0.2            | 1    | 7.9 | N   |
| 25a | N Y Y Y      | 61            | 2011          | 145/80          | 98              | 23         | 1300| 35          |                 |     |     |     | Yb   | Yb   | Yb  | Yb  | Yb   | Yb  | Yb               |
| 26  | N Y Y Y      | 39            | 2011          | 150/80          | 137             | 30         | 1081| 0.22        | 0.62           | 5    | 0.47|
| 27a | N N N N      | 48            | 2011          | 140/80          | 152             | 34         | 710 | 0.6         | 1.3            | 6.9  | 25.2| 0.72|
| 28a | Y N N N      | 55            | 2012          | 125/80          | 152             | 33         | 473 | 0.51        | 1.5            | 8.2  | N   | N   |

Patient data: *— no matched control available. F: female, M: male, TRPL: kidney transplantation, CKD: Chronic kidney disease, GFR: measured glomerular filtration rate, BP: blood pressure, Hb: hemoglobin value in g/L, Alb: serum albumin (in some cases protein was measured: P) g/L, Crea: creatinine in umol/L, Alat / Asat / ALP, values measured in μCat/L bilirubin (bil) measured in μmol/L. Liver values reported as normal was estimated (shown in italics). Yb: Oral cancer, Yc: Skin cancer, Yd: Hodgkins Lymphoma.
For the total study population of 28 patients, the average time of follow-up was 16.9 ± 2.1 years (minimum 1.24 and maximum 34.3 years). 23 patients were alive at the time of follow up, but five had died at ages of 67.0 ± 5.1 years. Over the long observation period, three patients with end stage renal disease (ESRD) and hemodialysis died at the age of 70 ± 9 years after 11.9 ± 2.5 years on dialysis.

One patient who never required dialysis died 24 years after the intoxication at the age of 65. Another patient died 19.1 years after the intoxication and 16 years after a successful kidney transplant at the age of 61. Fourteen patients were transplanted and of these three had a second kidney graft 12–15 years after the first one. The average age at the time of the accidental intake of poisonous mushrooms was 40 ± 3 years (\(n = 28\)), and 64% of patients were male. In the study group, 3 of the 16 transplanted patients developed cancer in the form of lymphoma, oral or skin cancer. Information of the specific cancer diagnosis was not available for the case control group.

**Acute effects**

The serum creatinine of the patients requiring dialysis peaked at 1329 ± 133 \(\mu\)mol/l (\(n = 15\)) and serum urea reached 31 ± 3.5 mmol/l (\(n = 11\)). The peak creatinine and urea values were markedly lower in patients that did not require dialysis, Table 1. Laboratory tests did not show signs of damage in any other organ apart from the kidney. Thus, the aspartate amino transferase (ASAT), alanine amino transferase (ALAT), alkaline phosphatase (ALP) and bilirubin values were all within their normal limits in the patients analyzed; 0.35 ± 0.04 \(\mu\)Cat/l, 0.34 ± 0.04 \(\mu\)Cat/l, 2.38 ± 0.04 \(\mu\)Cat/l, and 7.59 ± 0.5 \(\mu\)mol/l respectively (n \(n_{\text{ALAT}} = 14, n_{\text{ASAT, ALP, bilirubin}} = 18\)).

**Patients with non-dialysis dependent kidney injury**

Six of the patients that were orellanine intoxicated developed a less severe kidney injury and never required dialysis. On average their serum creatinine peaked at 474 ± 117 \(\mu\)mol/l (\(n = 3\)) during the first week. Initially, two patients were treated with three sessions each of hemoperfusion with charcoal, which in 1979 was suggested as therapy. One patient initially required dialysis and had a serum creatinine of 1270 \(\mu\)mol/l, but regained part of her renal function within the first month, and had a glomerular filtration rate of 87 ml/min 1 year later determined by \(^{51}\)Cr-EDTA clearance. The 7 patients who did not develop CKD5 were followed over a time-period of 18.3 ± 5.8 years, range 1.2–34.3 years.

**Patients with dialysis-dependent chronic kidney disease stage 5**

One month after the intoxication, 21 of 22 patients still required dialysis. 14 of them were transplanted, 6 received a kidney graft from a living donor and 8 from a dead donor. Before transplantation, the patients had been on dialysis for 19 ± 4 months (range 7–64 months). Three renal grafts lost their function after 11, 12 and 15 years and a second kidney transplantation was performed. Those patients now have been living with their 2nd grafts for 10, 11 and 15 years, Table 1.

**Kidney morphology**

Kidney biopsies were obtained from 5/28 patients. The biopsy material from one patient could not be retrieved and thus material was available from 4 patients. According to clinical data biopsies were obtained 10–21 days after fungal ingestion. All biopsies showed a similar pattern dominated by acute tubular necrosis (ATN), Fig. 2. Two patients (no 5 and 28) showed less severe damage with focal involvement, while the other two biopsies (no 20 and 24) showed a diffuse involvement with generalized inflammation and tubular damage. These biopsies also showed tubular dilatation, tubular cellular atrophy and degeneration, Table 2. All biopsies contained some apoptotic bodies, interstitial edema and focal inflammation but no eosinophilia. Fibrosis was not a prominent finding.

**Case control population**

The case control patients were age and sex matched, and they started dialysis or were transplanted in the same year as the patients in the study population, Table 3. No acceptable case control could be found for three of the 16 transplanted study patients since the candidates were either too old or had systemic disease. The distribution of kidney disease within the population is displayed in Table 3. In total, 20 patients were matched,
7 of the patients were on dialysis and the remaining 13 patients were transplanted, one of them twice. Of the 20 patients, 6 died at a mean age of 67.5 ± 4.7 years after 16.9 ± 6.6 years on dialysis (n = 3, at a mean age of 68 years) and 10.3 ± 2.2 years after transplantation (n = 3, at a mean age of 66 year), Fig. 3. In the case control population, one patient died of cancer and three other patients developed tumours during the observation period.

**Table 2** Renal morphology of biopsies from patients with Cortinarius poisoning

| Patient No. | Time after ingestion | Tubular damage: Necrosis, apoptosis, degeneration, dilatation, involvement | Edema | Inflammation | Fibrosis |
|-------------|----------------------|------------------------------------------------------------------------|-------|--------------|---------|
| 5           | 2v                   | 0 + 0 0                                                                | focal | minimal      | minimal |
| 7           | –                    | —                                                                      | —     | —            | —       |
| 20          | 3v                   | + + + +                                                                | diffuse | severe | prominent | minimal |
| 24          | >10d                 | 0 + + +                                                               | diffuse | prominent | slight  | slight  |
| 28          | 10d                  | 0 + 0 0                                                               | focal | focal       | minimal | minimal |

**Comparisons between study and control populations**

Of the 21 patients with ESRD in the study group, 20 were matched; 7 in dialysis and 13 that were transplanted. Cancer was not more frequent in the study group compared to control group. There were 3 cases of cancer in the study population of 21 patients (14%), of which all 3 were transplanted. In the control group 3 out of 20 (15%) were diagnosed with cancer, two of which were transplanted and one which remained in

**Table 3** The table describes the demographic data available for the matched control cohort*second transplant in 2003

| No#: Born year | Transplant 1 | Diagnosis                  | Follow up M | Follow up Y | Death Y | CoD | Cancer |
|----------------|--------------|----------------------------|-------------|-------------|---------|-----|--------|
| A. Matched control patients who had hemodialysis | | | | | | | |
| 1              | 1935         | 1980                       | PCK         | 356         | 30      | 2010 | Peritonitis | Y |
| 2              | 1925         | 1986                       | Amyloidosis  | 95          | 8       | 1994 | Unknown     | Y |
| 3              | 1965         | 2002                       | Crescentic GN | 141         | 12      | N   |           | N |
| 4              | 1953         | 2012                       | IgAN         | 20          | 2       | N   |           | N |
| 5              | 1958         | 2012                       | PCK          | 22          | 2       | N   |           | N |
| 6              | 1955         | 2009                       | PCK          | 59          | 5       | N   |           | N |
| 7              | 1942         | 1983                       | Pyelonephritis | 368         | 31      | N   |           | N |
| 8              | 1972         | 1988a                      | PCK          | 307         | 26      | N   |           | N |
| 9              | 1970         | 2000                       | Interstitial Nephritis | 156         | 13      | N   |           | N |
| 10             | 1973         | 2001                       | IgAN         | 194         | 16      | N   |           | N |
| 11             | 1952         | 1992                       | IgAN         | 157         | 13      | 2005 | Epilepsy | N |
| 12             | 1951         | 1992                       | Interstitial nephritis | 263         | 22      | N   |           | N |
| 13             | 1971         | 1992                       | CGN          | 260         | 22      | N   |           | N |

| B. Matched control patients who had a renal transplantation | | | | | | | |
| No#: Born year | HD start | Diagnosis                  | Follow up M | Follow up Y | Death Y | CoD | Cancer |
|----------------|----------|----------------------------|-------------|-------------|---------|-----|--------|
| 14             | 1925     | 1984                       | CVD         | 160         | 13      | 1997 | Cancer | Y |
| 15             | 1916     | 1984                       | Hereditary nephropaty | 139         | 12      | 1996 | Sepsis  | Y |
| 16             | 1962     | 1985                       | Glomerulonephritis | 343         | 29      | Y   |         | Y |
| 17             | 1942     | 1987                       | CVD         | 72          | 6       | 1993 | CVD   | Y |
| 18             | 1965     | 1990                       | Glomerulonephritis | 284         | 24      | N   |         | N |
| 19             | 1952     | 1999                       | Glomerulonephritis | 178         | 15      | N   |         | N |
| 20             | 1973     | 2011                       | Interstitial nephritis | 29          | 2       | N   |         | N |

*Second transplant in 2003, M: months, Y: year, PCK: polycystic kidney disease, Crescentic GN: crescentic glomerulonephritis, IgAN: IgA nephritis, CGN: Chronic glomerulonephritis, CoD: cause of death, CVD: cardiovascular disease
The cohort was matched based on age, sex and A. initiation of hemodialysis or B. renal transplantation
dialysis. In total, 4 patients of 21 with ESRD died in the study group compared to 6 in the control group, see Fig. 3. There was no statistical difference between survivals in the study group compared to the control group.

Discussion
The present study was done to reveal if patients that accidentally ingested deadly webcap (Cortinarius rubellus) suffered from long-term increases in morbidity or mortality. Indeed, 75% of the 28 patients developed CKD5, and 70% of them were transplanted. However, we did not find evidence of any other damage apart from the severe kidney injury. It should be noted that this is still a small patient group and of 39 cases we were only able to investigate 28 cases. Possible confounders could be the limited size of the study or that bias was introduced by co-morbidities or other medication. However, we do not anticipate that this has affected the outcome of the study.

The follow up period after the accidental intake of poisonous webcap is quite long, 16.9 years, with a range of up to 34.3 years. As expected, the long-term survival was excellent after transplantation as reflected by the current follow up period of 19.0 ± 2.5 years for the 14 patients in that group. The result is in accordance with previous reports over shorter periods of follow up [17, 22]. Regarding dialysis, it is well known that the mortality is high for all age groups [23]. Naturally, the survival on dialysis will depend, not only on the dialysis practice, but also on the underlying disease and on comorbidities [23–25]. The outcome was quite good for the study population on dialysis, which so far has been followed for 12.4 ± 3.4 years. Some patients have died over the three and a half decades of follow up. However, the patients on dialysis died after more than 12 years of treatment with haemodialysis at a mean age of 68. A similar picture was found in the case control population with follow up periods for transplanted patients of 15.2 ± 2.8 years and of patients on dialysis for 14.4 ± 3.5 years. In the case control population there were three deaths in each of the two ESRD groups, with transplanted patients being 66 years at the time of death, and patients on dialysis being 68. We found no evidence of increased risk for malignancy, endocrinological disorders or other morbidity in the study population.

Conclusion
We conclude that the long-term outcome is equally good for patients that have lost their renal function due to accidental intake of deadly webcap compared to other reasons for the uraemia. This was true both for transplanted patients and patients treated with dialysis.

Abbreviations
51Cr-EDTA: 51 Chromium-Ethylenediaminetetraacetic acid; ALAT: Alanine amino transferase; ALP: Alkaline phosphatase; ASAT: Aspartate amino transferase; ATN: Acute tubular necrosis; CKD5: Chronic kidney disease stage 5; ESRD: End stage renal disease; SEM: Standard error of the mean

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Availability of data and materials
No data has been submitted to any open access databases. Full patient records are being kept coded.

Authors’ contributions
BH and JN outlined the study design. HH, IH, JM, BH, JN conducted the study, JH and BH contacted and informed the patients and JM performed immunohistochemistry staining. HH, KE, BH, JN analysed the data and drafted the manuscript. HH, JH, JM, KE, BH, JN wrote and finalized the manuscript and provided critical review. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests. HH, BH, JN are in a commercialized project investigating the possibility of using orellanine as a treatment for metastasizing renal clear cell carcinoma. The funders listed in Acknowledgements had no role in study design, data collection and analysis, decisions to publish, or preparation of the manuscript.

Consent for publication
Not applicable.

Ethics approval and consent to participate
This study was conducted in accordance with the declaration of Helsinki and with the approval of the local ethical board of West Sweden in Gothenburg. The approval number is 1017-12.

All patients included in the study was informed both orally and in written form and patients who chose to participate signed a written consent form before participating.

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