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Inhaltsangabe

1. Originaler Artikel

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RESEARCH ARTICLE

Outcome and clinical course of EHEC O104 infection in hospitalized patients: A prospective single center study

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Abstract

Objectives

Shiga-toxin producing O157:H7 Entero Haemorrhagic E. coli [STEC/EHEC] are the most common cause of Haemolytic Uraemic Syndrome [HUS] related to infectious haemorrhagic colitis. Nearly all recommendations on long term treatment of EHEC infections refer to this strain. The 2011 outbreak in Northern Europe was the first of this dimension to be caused by the serotype O104:H4. We report on the 3.5 year follow up of 61 patients diagnosed with symptomatic EHEC O104:H4 infection in spring 2011.

Methods

Patients with EHEC O104 infection were followed in a monocentric, prospective observational study at four time points: 4, 12, 24 and 36 months. These data include the patients' histories, clinical findings, and complications.

Results

Sixty-one patients suffering from EHEC O104:H4 associated enterocolitis participated in the study at the time of hospital discharge. The mean age of patients was 43 ± 2 years, 37 females and 24 males. 48 patients participated in follow up 1 [FU 1], 34 patients in follow up 2 [FU 2], 23 patients in follow up 3 [FU 3] and 18 patients in follow up 4 [FU 4]. Out of 61 patients discharged from the hospital and included in the study, 54 [84%] were examined at least at one additional follow up. Serum creatinine decreased significantly between discharge and FU 1 from 1.3 ± 0.1 mg/dl to 0.7 ± 0.1 mg/dl [p = 0.0045]. From FU 1 until FU 4, no further change in creatinine levels could be observed. The patients need of antihypertensive medications decreased significantly [p = 0.0005] between discharge and FU 1 after four months. From FU 1 until FU 3, 24 months later, no further significant change in antihypertensive treatment was observed.

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Conclusions

Our findings suggest that patients free of pathological findings at time of discharge do not need a specific follow up. Patients with persistent health problems at hospital discharge should be clinically monitored over four months to evaluate chronic organ damage. Progressive or new emerging renal damage could not be observed over time in any patient.

Introduction

In 2011, Germany experienced the largest recorded outbreak of Entero Hemolytic Escherichia coli [EHEC] O104 associated enterocolitis to date, with fenugreek sprouts from Egypt as a possible causative source of infection [1]. More than 2900 patients were recorded by the Robert Koch Institut [RKI] facing health institutions with a huge battle against this epidemic [1]. The outbreak differed from formerly described outbreaks. It was caused by the O104:H4 strain of E. coli, which was characterized by expression of Shiga-toxin 2 and "Extended Spectrum b-Lactamase" [ESBL] [2]. Only two minor outbreaks of EHEC O104:H4 had been reported previously. The largest number of EHEC related outbreaks described so far were associated to the O157:H7 strain [3, 4]. To better outline the genetic specialities of the O104:H4 strain, Brzuszkiewicz et al. proposed the new term Entero Aggregative Hemorrhagic Escherichia coli [EAHEC] [5, 6]. The combination of shiga toxin production, ESBL status and increased adhesive capabilities resulted in unique epidemiologic and clinical findings. The predominance of young, female patients with high complication rates were markedly different to previous episodes of EHEC infections [7].

One of the major complications of EHEC gastroenteritis, Hemolytic Uremic Syndrome [HUS], was experienced by 25% of the patients during this epidemic [8]. HUS, originally described in 1955, is characterized by "the triad of acute renal failure, hemolytic anemia, and thrombocytopenia"[9], typically emerging in children [10]. This outbreak differed from previously described O157:H7 outbreaks concerning the incidence of HUS complication, where it appeared in 7% of mature patients [11]. Female adults were affected the most [68%], while only sporadic cases of infected children were found [8]. Neurological complications occurred with a high prevalence, ranging from seizures, paraplegia to also psychiatric syndromes such as anxiety and hallucinations [12, 13]. Treatment of EHEC related enterocolitis remained symptomatic, while intensified treatment of HUS and HUS related complications by plasmapheresis and dialysis were founded on empiric data, drawn from case series and retrospective analysis. The 2011 EHEC O104:H4 outbreak offered the unique chance to verify these assumptions. Prospective follow up of the acute courses of different patient cohorts resulted in a fundamental change of treatment algorithms. Substitution of intravenous fluids and plasmapheresis represented the therapeutical hallmarks of EHEC related HUS. After short term evaluation of treatment related outcomes of acute HUS, plasmapheresis demonstrated no significant benefit [14]. The previously described negative effect of antibiotic treatment was not observed [15] but instead, selected antibiotic treatment seemed to be beneficial for patients recovery [14].

The vast majority of publications on EHEC related diseases focus on clinical manifestations and courses of the acute phase of the infection [2,6,7]. Only few publications provide detailed follow-up data on well characterized, adult patients and in particular suffering from the O104:H4 strain [16,17]. However, this data is of high interest, as the influence of current treatment concepts have never been evaluated prospectively on long term outcome.

We describe the clinical course of 61 patients with EHEC related hemorrhagic enterocolitis in 2011 over a period of 3.5 years. The manuscript focuses on the long-term outcomes and complications.

Materials and methods

Patients

All patients included in this study suffered from EHEC O104:H4 associated enterocolitis during the 2011 outbreak and were treated in a single center as described earlier [7]. First patients were admitted to the hospital on the 14th of May 2011. A total of 61 patients with bloody and /or painful diarrhea due to EHEC O104:H4 enterocolitis were hospitalized. All 61 patients were included in this study. Inclusion criteria were diarrhea (≥3stools/24 h) at time of admission, positive stool testing for EHEC O104:H4 and/ or signs of HUS. HUS was defined as rise of serum creatinine above > 0,5mg/dl, thrombocytopenia <150/nl, signs of hemolysis with anemia, and appearance of schistocytes (Michael M et al, 2009 am Journal Kidney Dis). Patients' history, treatment and medication, general and abdominal symptoms, physical findings, frequency and quality of stool, blood chemistry, ultrasound, and radiologic findings were collected on admission, discharge, and at the defined time points of follow up. Laboratory data for all patients were recorded at least every second day, in case of HUS daily. All patients gave their written informed consent for this prospective study. The study protocol was approved by the ethical committee of the Chamber of Physicians, Hamburg, Germany [No.: 1123–2011].

Follow-up and data collection

Patients were repeatedly seen at four follow-ups [FU] [4, 12, 24 and 42 months after hospital discharge]. Blood, urine and stool samples were collected from each patient and analyzed by the Institut für Klinische Chemie of the Universitätsklinikum Hamburg-Eppendorf and MEDILYS, Laborgesellschaft mbh. Data on the patients' medical history, drug intake, side effects, physical inspection and blood pressure were documented through a standardized written survey and an additional interview. During all four follow-ups, stool cultures for EHEC were collected three times per patient. Samples were screened for their ESBL presence as well as the presence of Shiga-toxin 1, Shiga-toxin 2, and Intimin-gene using PCR. Further, all stool samples were tested for additional enteropathogenic bacteria and viruses, being other pathogenic E. coli, Salmonella, Campylobacter jejuni, Clostridium, Shigella, and Noro2/Adenovirus. Patients who did not consistently attend the follow-ups, were interviewed via phone by a standardized questionnaire after 42 months "Fig 1" "S4 Fig".

Statistical analysis

Clinical data of the study population are described by number of patients and percentage [categorical data] or by mean and SD [continuous data]. Student's *t*-test was performed to compare datasets. Differences were considered significant at $p<0.05$.

Results

Patients

Sixty-one patients were included in the study at the time of hospital discharge. All patients suffered from proven EHEC O104:H4 associated enterocolitis, 59% [n = 36] developed EHEC related HUS during their hospital stay. Patients had no signs for persisting enterocolitis or HUS when discharged from the hospital. Mean age of patients was 43 ± 2 years, 37 females and 24 males. Forty eight patients participated in FU 1 [75%], 34 in FU 2 [56%], 23 in FU 3

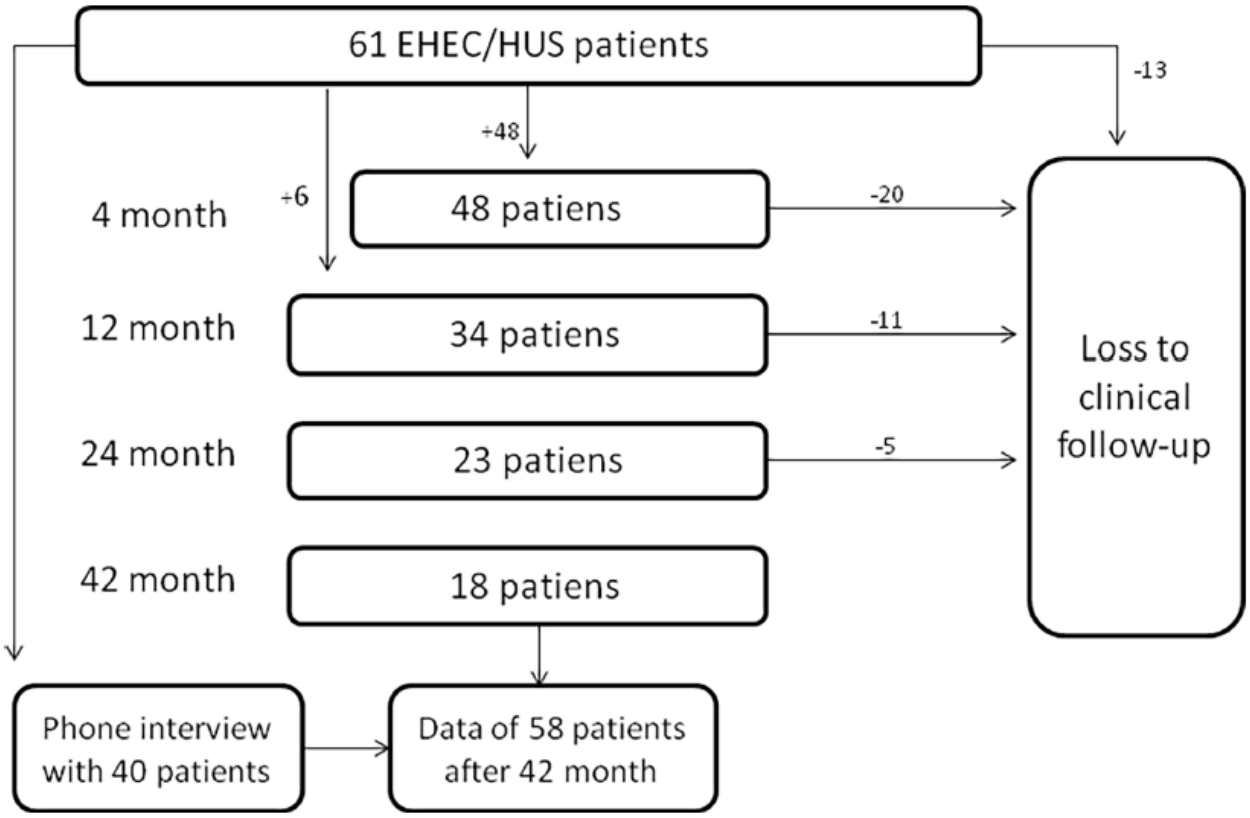

Fig 1. Schematic overview of the follow-up.

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[38] and 18 patients in FU 4 [30%]. 54 out of 61 study patients [88%] were examined at least at one time point after discharge. 44 out of 61 study patients [72%] attended at least two follow-ups. The mean number of follow-ups attended by each patient was 2.3. Patients, who did not attend to one of the follow- ups as well as patients who did not attend FU 4, were interviewed by phone after 42 months. Six patients dropped out due to lack of interest for the follow up over time and one patient was not able to communicate properly via phone because of severe neurological damages.

Patients characteristics at hospital discharge

At hospital discharge, 40.1% of the patients [n = 25] took one or more antihypertensive drugs "Fig 2" compared to 13.1% at hospital admission [n = 8] [80% of them suffered from HUS]. The mean systolic blood pressure was 130 ± 3 mmHg, the mean diastolic blood pressure was 77 ± 1 mmHg in all patients at hospital discharge "Fig 3". Mean serum creatinine was 1.3 mg/dl in all patients "Fig 4". Mean eGFR was 52 ml/min/1,73m^2 in all patients "Fig 5". Patients that suffered from HUS during their hospitalization had higher serum creatinine levels [1,56 mg/dl vs. 0,73 mg/dl], lower eGFR [32 ml/min/1,73m^2 vs. 75 ml/min/1,73m^2] and higher need of antihypertensive treatment, compared to patients who did not suffer from HUS [56% vs. 19%] "Figs 2, 4 and 5". One patient suffered from cortical blindness and another patient from severe

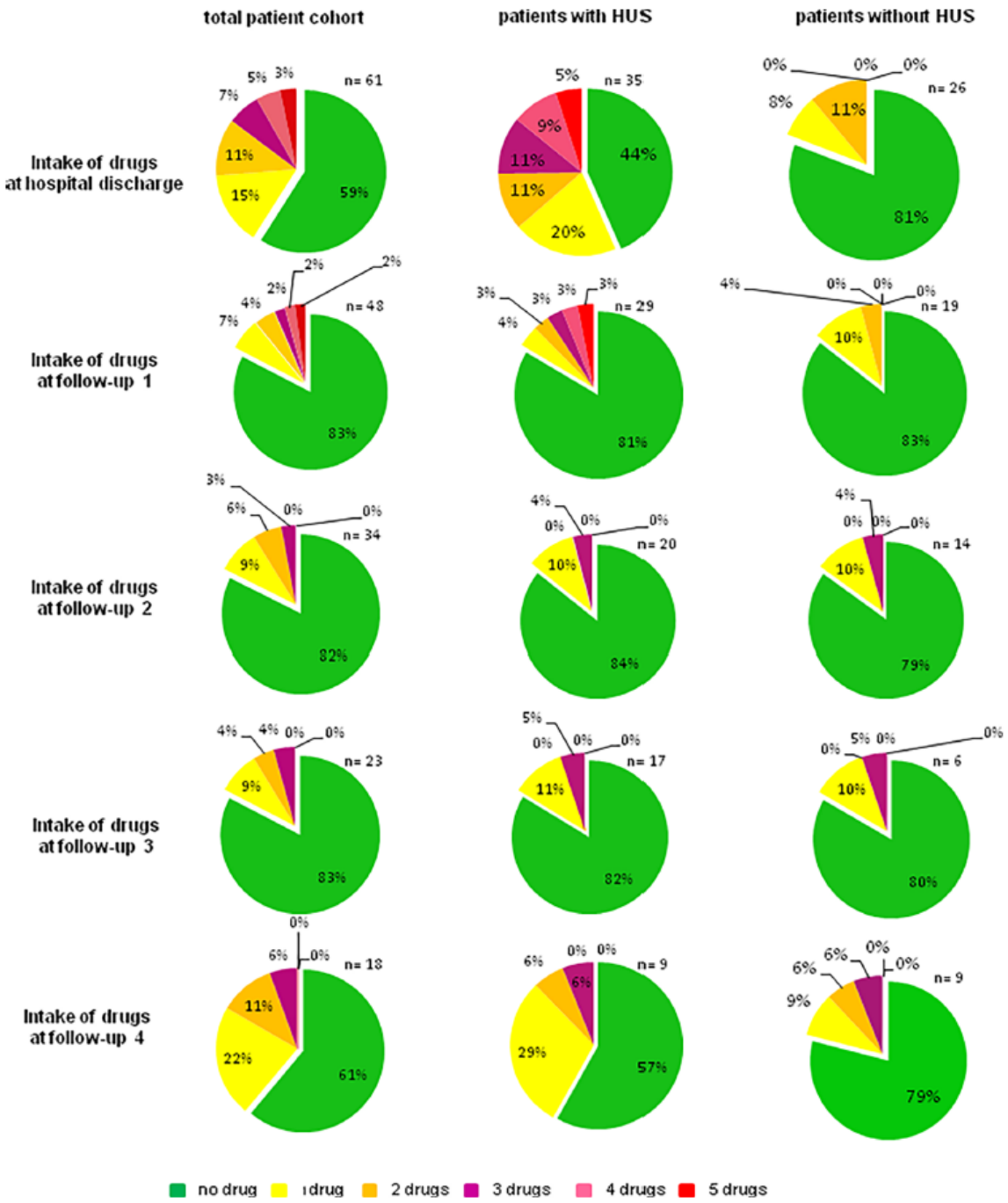

Fig 2. Overview of intake of antihypertensive drugs of patients with EHEC infection. Number of antihypertensive drugs of patients that suffered from EHEC infection with or without HUS, at the time of their hospital discharge.

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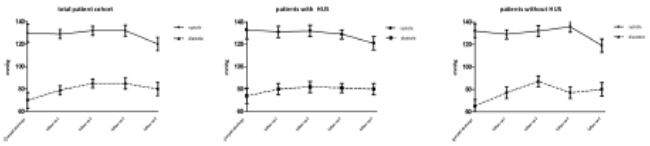

Fig 3. Trend of systolic and diastolic blood pressure. Patients that suffered from EHEC infection with or without HUS, at the time of their hospital discharge. FU 1 (4 month, n = 48), FU 2 (12 month, n = 34), FU 3 (24 month, n = 23) and FU 4 (42 month, n = 18) (mean ± SD).

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neurological impairment. In addition most patients [n = 51] had different minor symptoms ranging from abdominal pain to vision disorders. This data has been published earlier [7].

Prospective follow-up

Forty eight out of 61 patients [75%] were evaluated at FU 1 as described above. The mean age of patients was 40 ± 2, 26 females and 20 males. In all patients serum creatinine had declined significantly after 4 month from 1.3 ± 0.1 mg/dl to 0.7 ± 0,1 mg/dl [p = 0.0045] and eGFR increased from 52 ± 5 ml/min/1,73m^2 to 74 ± 4 ml/min/1,73m^2 [p = 0.0012], compared to hospital discharge. In the patient group that suffered from HUS, the decrease of creatinine and increase of eGFR was significantly higher as demonstrated in Figs 4 and 5. Patients that did not suffer from HUS had lower overall creatinine and higher eGFR levels at hospital discharge and four month later no significant reduction could be observed. From follow-up 1 until the last follow-up after 42 month, no further significant changes in creatinine and eGFR levels were observed.

The patient's need of antihypertensive medications dropped significantly [p = 0.0005] over the time period of four months after their release from hospital care. Only 17% [n = 8] of the total patient cohort still needed antihypertensive treatment at follow-up 1 compared to 40.1% [n = 24] at hospital discharge. The need of antihypertensive drug treatment decreased even more in the patients that suffered from HUS infection, from 56% to 19% of the patients in need of antihypertensive drugs at hospital discharge. Patients who did not suffer from HUS, had lower overall need of antihypertensive treatment at both time points [19% vs. 17%] shown in Fig 2. Between FU 1 and 3 no further significant change in antihypertensive treatment was observed [Fig 2]. At FU 4, the need of antihypertensive treatment increased again to 39% of all patients with 43% in the HUS patient group and 22% in the non-HUS patient group. Blood pressure monitoring showed no significant change in systolic and diastolic blood pressure over the whole period from hospital discharge to FU 4, indicating adequate antihypertensive treatment. At hospital discharge, mean blood pressure was 130 ± 3/79 ± 2 mmHg "Fig 3". Four months after hospital discharge, the mean systolic blood pressure was 129 ± 3/79 ± 2 mmHg

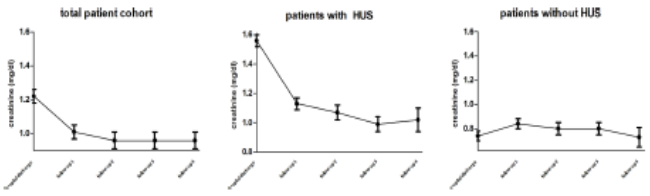

Fig 4. Trend of serum creatinine. Patients that suffered from EHEC infection with or without HUS, at the time of their hospital discharge. FU 1 (4 month, n = 48), FU 2 (12 month, n = 34), FU 3 (24 month, n = 23) and FU 4 (42 month, n = 18) (mean ± SD).

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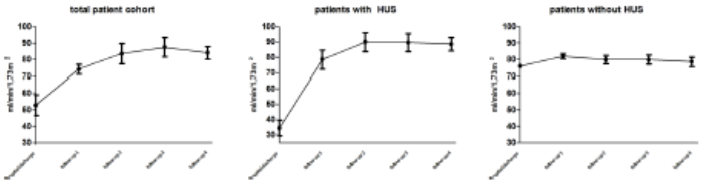

Fig 5. Trend of serum eGFR. Patients that suffered from EHEC infection with or without HUS, at the time of their hospital discharge. FU 1 (4 month, n = 48), FU 2 (12 month, n = 34), FU 3 (24 month, n = 23) and FU 4 (42 month, n = 18) (mean ± SD).

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[p = 0.51; 0,74]. Patients A and B were selected because of the correlation between high urine albumin, high serum creatinine and high blood pressure levels. "Figs 6 and 7" All other patients of the cohort had either normal urine albumin levels, or intermittent albuminuria with normal values on the next FU. The scatter plot of the albuminuria shows the distribution of elevated urine albumin levels, with most patients showing no elevated urine protein levels "Fig 8" "S1–S3 Figs".

Other therapeutic approaches of acute HUS, like plasma-separation, treatment with anti complement factor C5 antibody Eculizumab, and gut restricted antibiotic treatment with Rifaximin during their hospitalization, showed no differences in long term outcome. Many patients suffered from unspecific symptoms like concentration problems and fatigue with a decline of severity over time in both cases [concentration problems: 24% at FU1 vs. 6% at FU4; fatigue 9% at FU1 vs. 6% at FU4]. These findings were subjective data from the patient's interview and were not quantified. Neurological symptoms did not manifest or aggravate during FU. Severe neurologic deficits after HUS with central nervous system involvement in one patient remained unchanged over time.

Discussion

This observational study is the first to present data on the long term outcome of patients from the 2011 EHEC O104:H4 outbreak in northern Germany. Patients were observed up to 3.5 years after hospital discharge. A fairly positive outcome on renal function after one year FU has recently been published [18]. The need for longer FU periods was underlined [18, 19]. Our study observed patients from 4 months after hospital discharge up to 3.5 years. Kidney function and the need of antihypertensive treatment were nearly restored to normal after 4 months in both, the HUS and non-HUS patient group. Subsequent follow-up visits up to 3.5 years yielded no further significant changes in clinical and laboratory findings. This finding has to be interpreted with great caution, while the statistics were performed with a simple t test in a simple cohort. Besides this limitation, we still think, the t-test to be the most valuable statistical approach as an ANOVA analysis was not applicable because of the divergent data.

Recommendations for follow up examinations are missing and studies are highly variable in their methods of disease assessment and estimates of long-term prognosis. In a large pediatric cohort, hypertension and renal dysfunction aggravated on the course of 5 years after initial improvement [19]. Therefore our follow-up period could be still too short to draw conclusions on disease related organ damage. A Meta-analysis of a large patient cohort with diarrhea associated HUS without EHEC infection demonstrated that 25% of the patients developed chronic renal damage [20]. A previous study implied that the development of future hypertension correlates with the severity of the HUS syndrome [21]. Accordingly, patients of our cohort suffering from severe EHEC O104:H4 -infections and HUS, also developed aggravated hypertension and reduced kidney function.

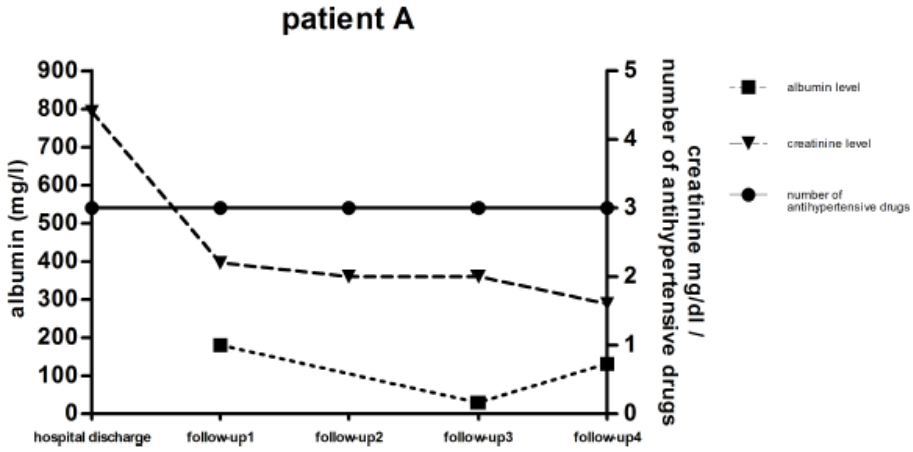

Fig 6. Trend of serum creatinine, urine albumin and antihypertensive drugs. Patient case of severe renal impairment at the time of hospital discharge. FU 1 (4 month, n = 48), FU 2 (12 month, n = 34), FU 3 (24 month, n = 23) and FU 4 (42 month, n = 18).

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In our cohort, renal function of severe and non-severe EAHEC cases had already assimilated at FU 1. Over the following period of 3.5 years, hypertension and renal function remained stable, or improved in all patients. These results are contrary to previous studies [22,23]. Patients suffering from HUS had a significant drop of creatinine levels and a significant increase in eGFR levels after 4 months. Even though creatinine levels remained slightly elevated, no further changes were noted at subsequent follow ups.

Aggravation of neurological disorders did not occur over the course of time in our patient cohort. Patients suffered from a lack of concentration and general fatigue. These conditions improved over time. These findings match with recently published data, concluding that long

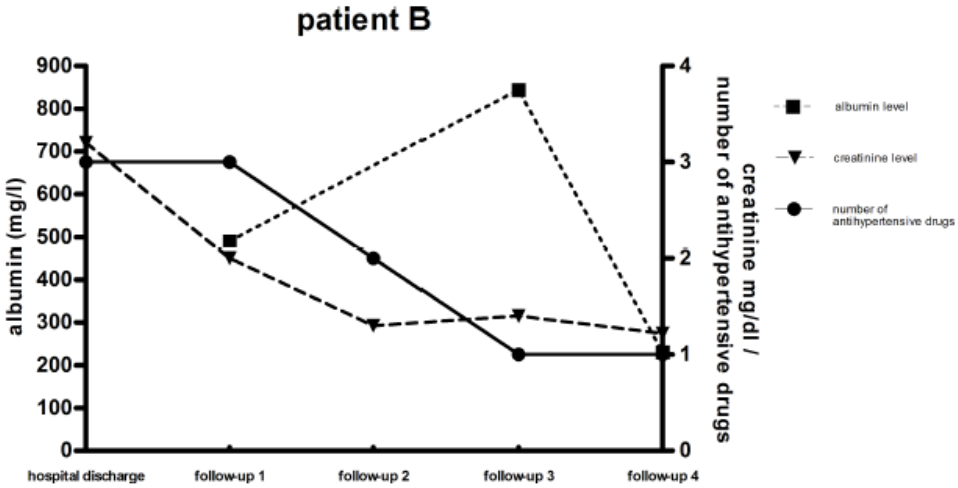

Fig 7. Trend of serum creatinine, urine albumin and antihypertensive drugs. Patient case of severe renal impairment at the time of hospital discharge. FU 1 (4 month, n = 48), FU 2 (12 month, n = 34), FU 3 (24 month, n = 23) and FU 4 (42 month, n = 18).

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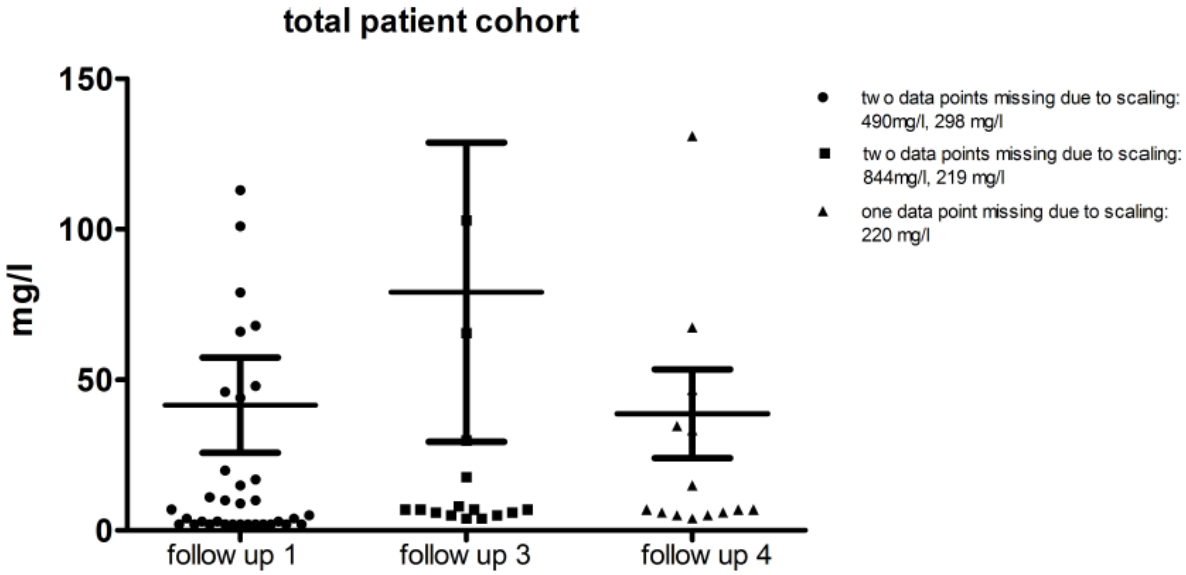

Fig 8. Trend of urine albumin levels of EHEC patients at the time point of their hospital discharge, FU 1 (4 month, n = 48), FU 3 (24 month, n = 23) and FU 4 (42 month, n = 18) (mean ± SD).

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term sequelae of EHEC O104:H4 associated neurological impairment in adults is rather positive [24].

One limitation of our long time follow-up was the inconsistent attendance to clinical visits: Out of 61 patients discharged from hospital and included in the study, 54 [88%] were examined at least once. Only 18 patients [29,5%] attended the last FU after 3,5 years. The mean number of follow-ups attended by each patient was 2.3. Patients who were free of symptoms were more often lost to follow up, compared to those with persisting complaints. However, regarding fatal outcome or severe complications, no differences were found between these two groups. Another limitation of our study was the rather small sample size, which excluded multivariate analyses. However we observed a clinical bias by patients with severe courses of disease being more compliant to follow-ups. Another limitation is the observational approach of the study. As no data was collected in a prospective setting, clinical data cannot be compared directly.

We conclude that during acute EHEC O104:H4 -infection, clinicians should focus on the multidisciplinary patient care, as described earlier [7]. Patients with normalized renal function and a good general state of health, do not need necessarily any further follow-up. Patients, who are discharged with manifest organ damage, need a close monitoring during the first four month to estimate the further health outcome. Patients with severe complications during EHEC O104:H4 -infection should be monitored longer with an individual time span to evaluate long term complications.

Supporting information

S1 Fig. Statistical analysis.
(DOCX)

S2 Fig. Patient data at hospital discharge.
(XLS)

S3 Fig. Patient data at follow-ups.
(XLS)

S4 Fig. Patients interviews by telephone.
(TIF)

Author Contributions

Conceptualization: J. P. Albersmeier, J. P. Bremer, W. Dammermann, S. Ullrich.

Data curation: A. M. Nielsen.

Formal analysis: J. P. Albersmeier, J. P. Bremer, A. M. Nielsen.

Investigation: J. P. Albersmeier, J. P. Bremer, C. Rüther, A. M. Nielsen, S. Ullrich.

Methodology: J. P. Albersmeier, J. P. Bremer, S. Ullrich.

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Validation: J. P. Albersmeier, J. P. Bremer.

Visualization: J. P. Albersmeier, J. P. Bremer.

Writing – original draft: J. P. Albersmeier, J. P. Bremer.

Writing – review & editing: J. P. Albersmeier, J. P. Bremer, W. Dammermann, S. Lüth, S. Ullrich.

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2. Darstellung der Publikation

Einleitung:

Im Sommer 2011 kam es in Deutschland zu einer Epidemie EAHEC (Entero-Aggregativer-Hämorrhagischer Escherichia coli) O104:H4 assoziierter Gastroenteritden. Von 2987 gemeldeten Fällen entwickelten 855 Patienten ein Hämolytisch-urämischen Syndrom (HUS) [1,2]. Die Epidemie galt am 26.07.2011 als offiziell beendet. Der Akutverlauf der Erkrankung wurde in mehreren Publikationen beschrieben, Daten zu den Langzeitverläufen von erwachsenen Patienten existieren jedoch kaum. Frühere Publikationen bezogen sich dabei vor allem auf den O157:H7 E.Coli Stamm, während dieser Ausbruch durch den O104:H4Stamm verursacht war [3]. Bis zu dem Ausbruch im Sommer 2011 gab es weltweit nur kleine Ausbrüche verursacht durch E.Coli O104:H4 [3].

Das besondere an diesem Stamm ist die gemeinsame Expression von Shiga-toxin 2 b- and ‘‘Extended Spectrum Lactamase‘‘ (ESBL) [2]. Gensequenzanalysen konnten zudem zeigten, dass der aktuelle Keim einen neuen Phenotyp darstellt, welcher die Eigenschaften von Enterohämorrhagische Escherichia coli (EHEC) und Enteroaggregative Escherichia coli (EAEC) kombiniert [4]. Dies könnte eine Erklärung für die starke Adhärenz des O104:H4-Stammes an die Kolonmukosa und die Verstärkung der Virulenz im Gegensatz zu anderen Escherichia coli-Stämmen sein. Brzuszkiewiczet al. schlugen deswegen den Terminus "Enteroaggregative-hämorrhagische Escherichia coli" (EAHEC) vor, um diesen neuen Phänotyp zu beschreiben [5].

Das Hämolytisch-urämischen Syndrom ist eine häufige und typisch Komplikation der EHEC-Infektion. Es wurde erstmalig 1955 beschrieben und ist durch die Trias hämolytische Anämie, akutes Nierenversagen, und Thrombozytopenie gekennzeichnet [6]. Die O104:H4 EHEC-Epidemie von 2011 hatte diesbezüglich einige Besonderheiten. Nicht nur die hohe Anzahl von Betroffenen insgesamt, sondern auch das häufige Auftreten des Hämolytisch-urämischen Syndroms, welches in 22,25% der Fälle vorlag, unterschied sich von zuvor beschriebenen EHEC-Infektionen [1,4]. In der Vergangenheit waren zu einem überwiegenden Anteil Kinder von großen Epidemien betroffen und entwickelten zudem ein Hämolytisch-urämisches Syndrom (45%). Bei den wenigen Epidemien erwachsener Patienten war ein Hämolytisch-urämisches Syndrom in nur sieben Prozent der Fälle nachweisbar [4,5].

Vor der hier beschriebenen Epidemie, gab es nahezu keine edvidenzbasierte Daten zu der Therapie von EHEC Infektionen und ihrer Komplikationen. Behandlungsempfehlungen basierten bis dato auf retrospektiven Analysen früherer Epidemien (vor allem des O157:H7 Stammes) und Schlussfolgerungen von In-Vitro-Analysen [6]. Der Nutzen einer antibiotischen Therapie der EHEC assoziierten Enterocolitis wird kontrovers diskutiert. Einige experimentelle Daten zeigen sogar, dass Antibiotika den Krankheitsverlauf durch eine verstärkte Shiga-Toxin Produktion negativ beeinflussen könnten [7]. Plasmapheresen für die Behandlung eines Hämolytisch-urämischen Syndroms wurden basierend auf empirischen Erfahrungswerten durchgeführt und sind durch die Deutsche Gesellschaft für Nephrologie in Fällen von neurologischen Komplikationen und/oder raschem Beginn eines Hämolytisch-urämischen Syndroms empfohlen [8].

2011 wurden 61 Patienten mit einer nachgewiesenen EAHEC O104:H4 Infektion der Asklepios Klinik Altona stationär behandelt, 59 % (n = 36) der Patienten entwickelten ein Hämolytisch-urämisches Syndrom [7]. Die Langzeitverläufe dieser Kohorte wurden über 42 Monate verfolgt. Chronische Folgen der Erkrankung wurden ermittelt und statistisch ausgewertet. Hier wird erstmalig der Krankheitsverlauf einer Patientengruppe über einen solchen Zeitraum nach einer EAHEC Infektion beschrieben.

Ziele:

Erstmalig wurden die Langzeitverläufe von 51 Patienten bezüglich Organschäden und Lebensqualität 42 Monate nach EAHEC 104:H4 assoziierter Gastroenteritis über einen Zeitraum von vier Jahren untersucht und ausgewertet. Ziel war es, Daten zu Spätschäden der Erkrankung zu erheben und Aussagen über die Notwendigkeit der Langzeitkontrolle treffen zu können.

Methodik:

Bei dieser Follow-up Studie handelt es sich um eine monozentrische, prospektive Beobachtungsstudie. Alle in die Studie inkludierten 61 Patienten hatten eine EHEC O104:H4 assoziierte Gastroenteritis. Einschlusskriterien waren Diarrhoen (≥3Stuhlgänge/24h), positive Stuhlproben auf EHEC O104:H4 und/oder klinische Anzeichen für ein Hämolytisch-urämisches Syndrom. Dies wurde definiert durch einen Kreatininanstieg >0,5 mg/dl, einer Thrombozytonpenie von 150 (10^3/µ)sowie der Präsenz einer hämolytischen Anämie.

Die allgemeinen Patientendaten, frühere Behandlungen und Medikationen, allgemeine und abdominelle Symptome, die Stuhlfrequenz- und Qualität, laborchemische Untersuchungen, sonographische und weitere radiologische

Untersuchungen wurde zum Zeitpunkt der Aufnahme, zum Zeitpunkt der Entlassung und zu festgelegten Nachuntersuchungszeitpunkten gesammelt. Die Verlaufsuntersuchungen fanden 4 Monate, 14 Monate, 24 Monate und 42 Monate nach Entlassung statt. An jedem Termin wurden die Patienten anamnestiziert und körperlich untersucht. Beschwerden, allgemeines Befinden und Belastbarkeit wurden mittels Fragebögen evaluiert. Stuhl- sowie Urin- und Blutproben wurden analysiert. Hierbei lag der Fokus besonders auf den Surrogatparametern einer chronischen Nierenschädigung und dem arteriellen Blutdruck. Patienten die nicht oder nur teilweise zu den Verlaufsuntersuchungen erschienen wurden mit einem standardisiertem Fragenbogen telefonisch interviewt.

Ergebnis:

Es zeigte sich, dass die Patientengruppe, die gesund entlassen werden konnte, auch in den Kontrolluntersuchungen als weiterhin gesund eingestuft wurde. Die Patienten welche mit eingeschränkter Nierenfunktion und/oder weiterhin erhöhtem Blutdruck entlassen wurden, konnten in den Nachkontrollen ihren Gesundheitszustand halten bzw. verbessern. Es kam in keinem Fall zu einer Verschlechterung von Nierenfunktion, Blutdruck oder des allgemeinen Gesundheitszustandes.

Die signifikante Verbesserung des Gesundheitszustandes konnte vor allem in den ersten vier Monaten nach Entlassung nachgewiesen werden. In den nachfolgenden Kontrollzeitpunkten wurden keine signifikanten Veränderungen mehr festgestellt. Ein Teil der Erkrankten (6%) gab über den gesamten Beobachtsungszeitraum persistierende abdominelle Beschwerden an. 24% der Patienten klagten über neu aufgetretene Konzentrationsstörungen zum Zeitpunkt des ersten Follow-ups, 9% gaben hier eine verminderte körperliche Leistungsfähigkeit nach der EHEC O104

Infektion an. Diese Beschwerden waren zum Zeitpunkt des letztens Follow-ups deutlich rückläufig (abdominelle Beschwerden: 6%; verminderte körperliche Leistungsfähigkeit: 6%). Einzelne Patienten klagten über persistente Hautveränderungen, Sehstörungen und eine veränderte Lichtempfindlichkeit.

Laborchemisch zeigte sich ein signifikanter Abfall der Kreatininkonzentration im ersten Follow-up, 4 Monate nach Entlassung. Zum Zeitpunkt der Entlassung aus der stationären Behandlung betrug die durchschnittliche Kreatininkonzentration 1,3 ± 0,1 mg/dl, nach 4 Monaten fand sich ein durchschnittlicher Serumkreatininspiegel von 0,7 ± 0,1 mg/dl. Die statistische Analyse der Anzahl der antihypertensiven Medikamente des Gesamtkollektivs zeigte zum Zeitpunkt des ersten Follow-ups nach 4 Monaten eine signifikante ($p = 0,005$) Reduktion der Antihypertensiva gegenüber der Entlassung bei insgesamt unverändertem Blutdruck. In den darauffolgenden Follow-ups konnten keine signifikanten Veränderungen der laborchemischen Untersuchungsbefunde gezeigt werden.

Schlussfolgerung:

Im Falle eines erneuten Auftretens der EAHEC-Infektion sollte die interdisziplinäre Versorgung der Patienten während der akuten Phase der Erkrankung im Vordergrund stehen. Ein Follow-up Intervall von 4 Monaten erscheint für den Großteil der Patienten ausreichend, jedoch erscheint bei Erkrankten mit einem komplikationsreichen stationären Verlauf ein individuell verlängertes Beobachtungsintervall sinnvoll.

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4. Zusammenfassung Englisch

Shiga-toxin producing O157:H7 Entero Haemorrhagic E. coli [STEC/EHEC] are the most common cause of Haemolytic Uraemic Syndrome [HUS] related to infectious haemorrhagic colitis. Nearly all recommendations on long term treatment of EHEC infections refer to this strain. The 2011 outbreak in Northern Europe was the first of this dimension to be caused by the serotype O104:H4. We report on the 3.5 year follow up of 61 patients diagnosed with symptomatic EHEC O104:H4 infection in spring 2011. Patients with EHEC O104 infection were followed in a monocentric, prospective observational study at four time points: 4, 12, 24 and 36 months. These data include the patients' histories, clinical findings, and complications. Sixty-one patients suffering from EHEC O104:H4 associated enterocolitis participated in the study at the time of hospital discharge. The mean age of patients was 43 ± 2 years, 37 females and 24 males. 48 patients participated in follow up 1 [FU 1], 34 patients in follow up 2 [FU 2], 23 patients in follow up 3 [FU 3] and 18 patients in follow up 4 [FU 4]. Out of 61 patients discharged from the hospital and included in the study, 54 [84%] were examined at least at one additional follow up. Serum creatinine decreased significantly between discharge and FU 1 from 1.3 ± 0.1 mg/dl to 0.7 ± 0.1 mg/dl [p = 0.0045]. From FU 1 until FU 4, no further change in creatinine levels could be observed. The patients need of antihypertensive medications decreased significantly [p = 0.0005] between discharge and FU 1 after four months. From FU 1 until FU 3, 24 months later, no further significant change in antihypertensive treatment was observed. Our findings suggest that patients free of pathological findings at time of discharge do not need a specific follow up. Patients with persistent health problems at hospital discharge should be clinically monitored over four months to evaluate chronic organ damage. Progressive or new emerging renal damage could not be observed over time in any patient. [PLoS One. 2018 Feb 8;13(2):e0191544. doi: 10.1371/journal.pone.0191544. eCollection 2018.]

5. Zusammenfassung Deutsch

Im Frühjahr 2011 kam es in Nordeuropa zur bisher größten Epidemie EAHEC (Entero-Aggregativer-Hämorrhagischer Escherichia coli) O104:H4 assoziierter Gastroenteritis. Insgesamt 855 Fälle des hämolytisch-urämischen Syndroms (HUS) und 2987 Fälle von akuter Gastroenteritis wurden gemeldet. Der Akutverlauf der

Erkrankung wurde in mehreren Publikationen beschrieben, Daten zu den Langzeitverläufen von Patienten existieren kaum. Hier wird erstmalig der Krankheitsverlauf einer Patientengruppe über einen solchen längeren Zeitraum berichtet. Bei dieser Follow-up Studie handelt es sich um eine monozentrische, prospektive Beobachtungsstudie. 61 Patienten mit einer nachgewiesenen EAHEC O104:H4 Infektion wurden in der Asklepios Klinik Altona stationär behandelt, 59% (n = 36) der Patienten entwickelten ein HUS, die Langzeitverläufe dieser Kohorte wurden über 42 Monate verfolgt. Chronische Folgen der Erkrankung wurden ermittelt und statistisch ausgewertet. Die Verlaufsuntersuchungen fanden vier Monate, 14 Monate, 24 Monate und 42 Monate nach Entlassung statt. Als gesund entlassene Patienten wurden auch in den Kontrolluntersuchungen weiterhin als gesund eingestuft. Die Patienten, welche mit eingeschränkter Nierenfunktion und/oder weiterhin erhöhtem Blutdruck entlassen wurden, konnten in den Nachkontrollen ihren Gesundheitszustand halten bzw. verbessern und es kam in keinem Fall zu einer Verschlechterung. Verbesserungen des Gesundheitszustandes wurden nur in den ersten vier Monaten der Nachbeobachtung beobachtet. Während den nachfolgenden Kontrollzeitpunkten blieb der Gesundheitszustand konstant. Laborchemisch zeigte sich ein signifikanter Abfall der Kreatininkonzentration im ersten Follow-up, vier Monate nach der Entlassung. Bei der Entlassung betrug die durchschnittliche Kreatininkonzentration 1,3 ± 0,1 mg/dl, nach vier Monaten fand sich ein durchschnittlicher Serumkreatininspiegel von 0,7 ± 0,1 mg/dl. Die statistische Analyse der Anzahl der antihypertensiven Medikamente des Gesamtkollektivs zeigte zum Zeitpunkt des ersten Follow-ups nach vier Monaten eine signifikante ($p = 0,005$) Reduktion der Antihypertensiva gegenüber der Entlassung bei insgesamt unverändertem Blutdruck. In den darauffolgenden Follow-ups konnten keine signifikanten Veränderungen der laborchemischen Untersuchungsbefunde gezeigt werden. In der Behandlung von EAHEC-Infektion sollte die interdisziplinäre Versorgung der Patienten während der akuten Phase der Erkrankung im Vordergrund stehen. Patienten, die gesund entlassen werden, brauchen kein spezielles Follow-up. Bei Patienten mit Organschäden bei Entlassung sind die ersten vier Monate wesentlich für die Wahrscheinlichkeit dauerhafter Schädigungen. Bei Erkrankten mit einem komplikationsreichen stationären Verlauf ist ein individuell verlängertes Beobachtungsintervall sinnvoll. [Abstract von Albersmeier auf dem Viszeralmedizin Kongress 2016 in Hamburg: 42 Monate nach EHEC O104:H4 - Outcome und klinische Verläufe einer monozentrischen Kohorte]

6. Erklärung des Eigenanteils

Die initiale Datenerhebung zum Zeitpunkt des EHEC Ausbruchs der Kohorte des Asklepios Krankenhauses Altona wurde von PD. Sebastian Ullrich, Dr. Jan Philipp Bremen und Frau Mette Nielsen durchgeführt, ebenso wie die klinische Visite der Patienten zu den Zeitpunkten der ersten drei Follow-Ups. Im vierten Follow-Up waren Jan Philipp Albersmeier und Dr. Jan Philipp Bremer verantwortlich für die Datenerhebung. Die Gesamtanalyse der Daten wurde von Dr. Jan Philipp Bremer, sowie Jan Philipp Albersmeier gemeinsam durchgeführt. Die statistische Analyse wurde durch Dr. Jan Philipp Bremer durchgeführt. Das Schreiben des gesamten Manuskriptes und die Anfertigungen der Figuren und Tabellen wurde von Jan Philipp Albersmeier allein durchgeführt. Beratend und Korrekturlesend waren hier PD. Sebastian Ullrich und Dr. Jan Philipp Bremer vornehmlich tätig, sowie teilweise Dr. W. Dammermann und PD. Stefan Lüth sowie Prof. Dr. Udo Schumacher. In der Phase des Review Verfahrens des Journals waren PD. Sebastian Ullrich und Jan Philipp Albersmeier gemeinsam in der Korrektur des Manuskriptes tätig.

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Zuletzt danke ich meiner Frau Marleen für die finale Korrektur und Unterstützung während dieser Dissertation.

8. Curriculum vitae

"Lebenslauf wurde aus datenschutzrechtlichen Gründen entfernt"

9. Eidesstattliche Erklärung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.
Ferner versichere ich, dass ich die Dissertation bisher nicht einem Fachvertreter an einer anderen Hochschule zur Überprüfung vorgelegt oder mich anderweitig um Zulassung zur Promotion beworben habe.
Ich erkläre mich einverstanden, dass meine Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.

Unterschrift: .....

(Jan Philipp Albersmeier)