Outpatient parenteral antimicrobial therapy in Germany: a prospective cohort study protocol

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ABSTRACT

Introduction Outpatient parenteral antimicrobial therapy (OPAT) means intravenous administration of antibiotics outside the hospital. The antibiotics are administered at the patient’s home. The advantages are the shortening of the inpatient stay, which means that patients can remain in their familiar environment, the reduction of nosocomial infections as well as the reduction of hospital and therapy costs. Nevertheless, OPAT is rarely performed in Germany, despite its international application. Therefore, systematic data on OPAT are not available in Germany. The project objective is to investigate the medical care using OPAT under medical, epidemiological and economic aspects within the framework of the Cologne Network of Infectious Diseases.

Methods and analysis Observational study with mixed-methods approach, qualitative analysis to identify physician-side factors to assess the attitude of general practitioners in Cologne with regard to possible implementation barriers of an OPAT. Longitudinal analysis of an OPAT patient cohort with respect to clinical and patient-relevant outcomes using descriptive and conclusive statistics.

Ethics and dissemination The study has been approved by the Institutional Review Board of the University of Cologne, Germany (19-1284-1). Written informed consent was obtained from all participants. The results will be submitted for publication in a peer-reviewed journal and presented at one or more scientific conferences.

Trial registration number NCT04002453.

BACKGROUND

Outpatient parenteral antimicrobial therapy (OPAT) describes the administration of an approved parenteral antibiotic therapy in a non-inpatient setting. For this purpose, a safe vascular catheter is generally inserted, through which the anti-infective therapy is administered as an infusion, for example, by using an elastomeric pump at (1) the office of a general practitioner or (2) a specialised outpatient facility, or (3) at the patient’s home. Outpatient therapy with intravenous antibiotics was first used in 1974 in children suffering from cystic fibrosis. Since then, this therapy has gained varying degrees of acceptance and is firmly established in the healthcare system in the USA, Brazil, Canada and Great Britain (GB). The growing acceptance of this treatment modality can be attributed to its advantages in shortening or even avoiding the hospital stay and its linked positive effects on patients’ quality of life and mental health. Moreover, studies have shown that OPAT reduces the risk of hospital-associated infections as well as the need for an inpatient stay or its duration and leads to cost savings in the public health sector.

In two retrospective cohort studies, OPAT was successful in 87.1%–92.4% of the conducted cases. Side effects such as adverse drug reactions (ADR) and line-related events or cases. Side effects such as adverse drug reactions (ADR) and line-related events or vascular access complications were reported in 7%–18% of all OPAT patients and occurred mainly in the first 14 days. Readmission rates beyond OPAT varied in different studies 9%–15%. Mortality rates were generally low. Risk factors for OPAT failure were female sex, comorbidities such as diabetes and renal failure, as well as treatment with
cancomycin or teicoplanin. However, due to its challenging nature, teicoplanin should not be given in the context of OPAT. Therefore, it is important that the indication for OPAT is critically reviewed and given by the attending physician, the infectious diseases specialist, trained nursing staff and a pharmacist in accordance with international guidelines. In addition, the clinical stability and compliance of the patient is crucial for a successful outpatient treatment. Further factors such as the infrastructure of the home environment and the patient’s social integration play an important role in the decision for OPAT. The choice of an anti-infective agent is made according to principles of rational antibiotic therapy. Finally, to ensure the successful completion of OPAT regular outpatient visits to a centre specialised in infectious diseases and holding OPAT expertise are necessary. Within these follow-up, visitations compliance and response to therapy are surveilled, ADRs and line-related events are ruled out.

As previously noted, OPAT is a standard form of therapy in some countries like the USA and GB. In contrast, there are only a few specialised centres in Germany that offer OPAT. General recommendations or established standardised care structures for OPAT do not yet exist in Germany. Therefore, a study is being conducted to test the feasibility of OPAT in Germany. It is intended to collect clinical, epidemiological as well as patient reported data (Patient-Reported Experience Measures and Patient-Reported Outcome Measures) and to assess the practicability of implementing OPAT by means of cross-sectoral cooperation of hospitals and resident physicians of different levels of care within the Cologne Network of Infectious Diseases (10 hospitals and resident physicians).

Aims of the study

The aim of this observational study is to test effectiveness, safety, logistics and acceptance of OPAT in the Cologne metropolitan area. The study generates reliable data identifying the need for OPAT and its feasibility in Germany, which are not yet available. The data will be used to create a model for a patient-centred outpatient form of care for anti-infective, intravenous therapy.

We also want to identify barriers preventing the implementation of OPAT in the German public health system, as well as the advantages and disadvantages of this therapy option regarding sociodemographics, patient satisfaction, treatment response and tolerability. The results are to be used in the further structural design of OPAT as a care option in the outpatient sector.

The following specific objectives are set:

1. Epidemiology
   - Generation of reliable data to point out the need for and feasibility of OPAT.
   - Demonstration of the distribution of infectious diseases treated with OPAT.
   - Characterisation of the patient collective suitable for OPAT.
   - Definition of risk factors for OPAT.
   - Collection of sociodemographic data.

2. Clinical course
   - Documentation of therapy response, therapy failure, therapy discontinuation, patient compliance, side effects, development of resistance, rehospitalisation, catheter-related events.
   - Highlighting organisational, technical, medical problems affecting the feasibility of OPAT.
   - Review of the doctor-patient interaction in the outpatient sector with an emphasis on the doctor’s and patient’s satisfaction.

3. Recommendations
   - Establishment of recommendations for the standardised implementation of OPAT.
   - Establishment of a model system for OPAT as a patient-centred outpatient therapy option.

METHODS/DESIGN

Patient population

Case number calculation and power calculation

Since this study is intended to determine whether the complex processes that are necessary for the OPAT in general are feasible and do work for the patient and the doctor, the number of cases has been set on the basis of previous studies. The sample size results from a prospective screening in 2017: about seven patients suitable for OPAT were examined monthly in the infectious diseases consultation service of the University Hospital of Cologne. With a supposed drop-out rate of about 15% and a rejection rate of 15% for the study thus results in a feasible sample size of 120 patients in 2 years of recruitment (7 × (24) × (0.85) × (0.85) = 121).

As no inferential statistical evaluations are intended, a power calculation is not possible. With its data collection and descriptive evaluation, the study can only be used as a basis for hypothesis formation as well as for giving first descriptive insights for further studies. Based on the data obtained in this study, it is possible to get a first impression of possible effect sizes and case numbers, planning for a following comparative study.

Inclusion and exclusion criteria

This study is open to all patients who are intended to receive an OPAT for at least 5 days. Only patients who are suitable for OPAT according to international guidelines and whose infections require intravenous therapy are considered for our study. Basically any infection can be treated with an OPAT as long as there are no comorbidities that require an inpatient stay. Patients must be clinically stable prior to discharge and be able to administer the antibiotics by themselves or with help from relatives or friends. Patients have to be at least 18 years old and must give written informed consent to participate in the study.
Patients who do not fulfill these requirements or are not capable of giving informed consent will not be able to participate.

### Study design

This prospective longitudinal observational study recruits patients from the inpatient area of the participating hospitals and resident doctors of the Cologne Network of Infectious Diseases who receive OPAT. An infectious disease consultation service is established in all participating centers of the network. Together with the attending physicians, a specialist in infectious diseases from the inpatient area of the hospital has established the indication for OPAT and the outpatient feasibility of OPAT has been examined.

After sufficient time for consideration and exclusion of all uncertainties, the patient signs the informed consent. If the patient does not want to undergo OPAT, he or she will be questioned anonymously in a short written survey about possible reasons that could have led to refusal. After giving informed consent, the patient is admitted to the study and his case will be reported to the study administration office. If the patient agrees in this consent form to also participate in the patient satisfaction substudy, conducted by the collaborating Institute for Medical Sociology, Health Services Research and Rehabilitation Science (IMVR), the study participant will be surveyed by written questionnaires at a maximum of 3 time points. Using the identifying data of the patients, the study staff generates two different patient pseudonyms, one for clinical data and one for the patient satisfaction survey. The originals of the declarations of informed consent remain at the study administration office, the patient receives copies of the consent forms.

Once the patient is discharged from hospital, a pharmaceutical care service takes over and provides the patient with the prescribed antibiotic medication. 2 times a week the care service checks the intravenous access. In case of any trouble with the application, the patient can call the care service or the ID specialist in charge at any time.

There are at least four measuring points (depending on the duration of the treatment) in the form of a study visit planned. At each of the measurement points, standardised documentation and the patient satisfaction survey (max. 3 questionnaires) will be performed. Measurement time 1 corresponds to the baseline visit (V1) at enrolment (figure 1). In the following, the contents of the respective study visits are listed.

#### Medical visit 1 = baseline:
1. Check of inclusion criteria of potential patients.
2. Patient’s information about the study.
3. Signing of the informed consent.
4. Inclusion into the study and reporting to the study centre, patient pseudonymisation by the central trust centre with no access to the database.
5. Application of the venous access, preferably PICC line. Patients who already have a port or dialysis catheter can use this access for OPAT, too.
6. Collection of basic data (table 1).
7. First questionnaire concerning patient satisfaction (table 2).

#### Medical visit 2 – x = follow-up visit:
1. Recording and documentation of medical parameters and handling of OPAT.
2. Second questionnaire concerning patient satisfaction (not applicable when the OPAT lasts less than 14 days).

Depending on the duration of the therapy, further visits will be scheduled at intervals of 7±2 days to the follow-up in progress. No further questionnaires are handed out during these visits.

#### Final visit:
1. Recording and documentation of medical parameters and handling of OPAT after final treatment.
2. Final questionnaire concerning patient satisfaction.

#### Longtime follow-up visit:

![Figure 1](image-url)  
**Figure 1** Scheme of therapy and study procedure. OPAT, outpatient parenteral antimicrobial therapy.
1. Recording and documentation of medical parameters 3–4 weeks after the end of the outpatient therapy.

**Data: collection, management and analysis**
The data, collected for each patient on paper forms (case report forms, CRFs), are documented in the OPAT study database. The study personnel gets personalised access.

The database is created using REDCap, a web application for building and managing online surveys and databases (Vanderbilt University), data are stored on local servers. Thereby regular data backups are carried out, authentication protocols and hierarchically organised access authorisations are used to protect the data from unauthorised access or loss.

Based on this data collection, a quantitative analysis regarding the treated infections is conducted. Data for the following parameters are raised:
- Sociodemographic factors (age, illness, comorbidities).
- Medical factors (therapy compliance, therapy response, side effects, rehospitalisation).
- Organisational factors (problems with drug delivery, catheter associated complications).

Patient satisfaction is measured and analysed both quantitatively and qualitatively (mixed methods). If the patients give their consent to be interviewed qualitatively (in person or per telephone) as well, the information in the questionnaire is used to identify patients who are invited to participate in an in-depth standardised structured interview. For this purpose, an explanatory sequential approach was chosen.

The evaluation of patient satisfaction (questionnaires and interviews) is independent of the treatment. The questionnaires will be sent by mail by the IMVR. The questionnaires are pseudonymised and data are automatically read in via TeleForm, a forms processing application (OpenText Corporation).

Using the patient’s pseudonym, the survey data can be linked with the therapy-related pseudonym by the central trust centre.

**Further analysis**
The direct evaluation at the patient level will be flanked by further surveys and analyses aimed at capturing the potential of OPAT and identifying possible implementation barriers.
Two focus groups (n=8 participants each resident and hospital physicians) are carried out (exploratory sequential design). Relevant factors as gender, education and professional experience are considered in the composition of the focus groups (purposeful sampling).

All individual interviews and discussions within the focus groups are digitally recorded, transcribed, pseudonymised and analysed with the consent of the participants. The results on the possible inhibiting or promoting factors of utilisation are the basis for the following questionnaire development for the survey of general practitioners.

Questionnaires for all general practitioners in the Cologne Metropolitan Area (approx. n=870) are being developed. The aim of this survey is to provide information about OPAT and to record the willingness to participate in OPAT and to identify implementation hurdles in the outpatient sector. In the long term, this is intended to promote and strengthen the cooperation between the outpatient and inpatient sectors. In the survey of general practitioners, an adapted version of the classic ‘Total Design Method’ will be applied according to Dillman with four postal survey waves to achieve a high return flow. Taking into account the expected return flow (approx. 30%), despite procedure according to Dillman, there is a need for a full census in order to be able to make representative statements.

**Measuring instruments: general practitioner survey**

The measuring instruments used to survey the general practitioners are literature-based and adapted based on the results of the focus groups.

Proposed variables:
- Relative number of patients who could use OPAT*.
- Setting for OPAT*.
- Experience in the treatment of patients with a long-term infection.
- Work experience, further training.
- Sociodemographic factors (eg, age and gender).
- Workload.
- Cost–benefit assessment.
- Doctor–patient interaction.

*Variable dependent on results of the qualitative analysis.

Statistical analyses are descriptive, summarising distributions of quantitative variables using valid count, mean, SD and percentiles (0, 25, 50, 75, 100) and distributions of qualitative variables using absolute and relative (%) frequencies. Subgroup analyses are done by gender, complication, catheter, for example. Association and/or interaction between variables may be explored by multivariable methods, for example, multiple linear, logistic or Cox regression.

An epidemiological and economic analysis of the current care situation and thus the relevance of OPAT is carried out based on the CoRe-Net database for the Cologne Metropolitan Region. This database contains the data of four statutory health insurance companies for the years 2013–2019 and thus covers approximately 50% of the statutory health insured persons living in Cologne. This regional database is suitable to provide epidemiological data on care of patients with long-term intravenous antibiotic therapy (number of patients, type of disease, therapy duration, therapy change). The data can also be used to determine clinical pathways and typical patterns of care. By comparison with a control group without long-term (intravenous) antibiotic therapy matched for age and sex (1:5) the associated excessive costs can be displayed quantitatively. By linking these results with small-scale sociodemographic indicators, we hope to show differences in care according to social stratification. In addition, it is to be examined whether influencing factors are recognisable that indicate regional inequalities in care (hypothesising). The results are suitable for developing models that point to cost savings and/or the change of cost types.

**Data protection**

In this observational study, two aspects need to be considered:

**Documentation of clinical data**

In the context of this observational study, medical data of study participants are surveyed. This includes general information on initiation, inclusion, planning, implementation of OPAT and the data mentioned above. These data are stored in the personal medical record and documented in the CRFs. In this observational study, anti-infective therapies approved for various infectious diseases are applied. An experimental approach is not used. Therefore, no advantages or disadvantages associated with participation in the study exist. Data that are relevant to the study are stored in pseudonymised form. Pseudonymised means that no names or initials are used, only a random number and/or letter code. The pseudonymisation is done by the central trust centre with no access to the database.

**Collection and analysis of the questionnaires**

Data raised from the surveys are also stored under an assigned pseudonym. Using the assigned pseudonym (study inclusion), the data collected during treatment can be linked to the survey data. The collected and pseudonymised data are processed by an electronic data system and statistically evaluated. The results are only presented in anonymous form. The personal data will be treated confidentially in accordance with the applicable data protection law.

Regular data backup, hierarchical management of authorisations and authentication protocols secure the database against unauthorised access and/or loss. The recorded audio is transcribed by an external company that is committed to data protection. All collected data are stored for a maximum of 10 years after publication of the results. The audio recordings and transcriptions are stored for a maximum of 10 years after publication of the
results. The observance of the Federal Data Protection Act and the State Data Protection Act of North Rhine-Westphalia, as well as the Health Data Protection Act of North Rhine-Westphalia is fully guaranteed. The study participants were informed about this and have agreed to voluntary participation.

**Planned start and end dates for the study**

Planned start: 1 July 2020.
Planned end: 30 June 2023.

**Patient and public involvement**

Patients and members of the Public were not involved in the design of this study.

**DISCUSSION**

The study will provide information on the feasibility, success concerning therapy outcome and patient satisfaction as well as cost of outpatient parental antimicrobial therapy in Germany. The results of the study may be useful for future health-service planning and will provide a foundation for future work to establish the OPAT in Germany and implement this therapy option into the German remuneration system.

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**Contributors**

NS, ChL, PI and CS made substantial contributions to the conception and design of the work. ChL built the database and was a major contributor in writing the manuscript. VB, CO, SP, AH, ClL, MH and HP substantively revised the work. All authors read and approved the final manuscript.

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**Competing interests**

None declared.

**Patient and public involvement**

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication**

Not applicable.

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**Open access**

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