Efficacy and safety of selective decontamination of the digestive tract (SDD) to prevent recurrent hepatic cyst infections in polycystic liver disease: a retrospective case series

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Background: Hepatic cyst infection is a complication of polycystic liver disease (PLD) that causes substantial morbidity. Repetitive infection is frequent and is increasingly difficult to treat. As translocated gut bacteria are considered the cause, we hypothesize that selective decontamination of the digestive tract (SDD) reduces recurrence of hepatic cyst infection.

Methods: We performed a retrospective, observational study in two referral centres. All patients with PLD treated with SDD for hepatic cyst infection were included. Efficacy was determined by calculating the infection incidence (hepatic cyst infections per month) before and during SDD therapy. Adverse events were scored according to the Common Terminology Criteria for Adverse Events (CTCAE).

Results: We identified eight patients who received SDD (88% female, 88% polycystic kidney disease). The median age was 65 years (IQR: 51–74 years). SDD lowered the median incidence from 0.09 episodes per month (IQR: 0.06–0.25 episodes per month) to 0.01 episodes per month (IQR: 0.00–0.05 episodes per month) (P = 0.12). Discontinuation of SDD led to rapid recurrence of cyst infection (71% within 6 weeks). SDD consisted of polymyxins with/without aminoglycosides. The median SDD treatment duration was 20 months (range: 3–89 months). Six patients (75%) developed adverse events [CTCAE Grade 1 (gastrointestinal: n = 3) or Grade 3 (ototoxicity: n = 1; fungal infection: n = 1)], mostly attributable to aminoglycosides; one patient developed polymyxin E resistance.

Conclusions: SDD prophylaxis provides a novel strategy for limiting recurrent hepatic cyst infection in PLD patients. However, adverse events are frequent and curtail its use. As most were attributable to aminoglycosides, polymyxin E is considered the preferred therapy.
Patients and methods

Ethics

This study was approved by the Institutional Ethical Review Board of Radboudumc (reference: 2019-6062) and Leiden University Medical Center (LUMC) (reference: 2019.057). We obtained informed consent from study participants.

Study design, setting and participants

Our retrospective, observational cohort study was executed in two referral centres for ADPKD/ADPLD (Radboudumc, Nijmegen, The Netherlands and LUMC, Leiden, The Netherlands). We considered PLD patients (aged ≥18 years) with a history of multiple (>2) hepatic cyst infections and who received at least one SDD dose as prophylaxis (polymyxins, neomycin and/or tobramycin; all oral use in tablet form). We reviewed all electronic patient records for these criteria using the search engine CTcue (CTcue B.V., Amsterdam, The Netherlands) and asked all physicians involved in caring for PLD patients to provide cases. Renal cyst infection patients were excluded. This study is reported according to STROBE guidelines. 

Outcome measures

Patient demographics and clinical course were extracted from electronic records. We recorded every diagnosis of hepatic cyst infection during follow-up. Diagnosis was made by the treating physician involved, based on clinical, biochemical, microbiological and imaging criteria, in addition to response to antimicrobial treatment. When hepatic cyst infection occurred within 1 month following the end of treatment of a previous cyst infection it was defined as: (i) persistence of the same infection when the cultured pathogen and resistance pattern matched with findings from the earlier infection; or (ii) as a new episode when different pathogens or distinct resistance patterns were found. Only those defined as (ii) were included in analyses.

An adverse event was defined as any unfavourable and unintended sign, symptom or disease temporally associated with SDD use that may or may not be considered related to SDD. Adverse events were scored according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 by the authors. Severity was graded as mild (Grade 1), moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4) or death (Grade 5). Beyond the scope of CTCAE, confirmed antimicrobial resistance following SDD was included separately.

Statistical methods

We calculated hepatic cyst infection incidence by dividing the number of episodes by the months of follow-up before and during SDD. To limit bias, the first episode during follow-up prior to SDD was omitted, as follow-up started with a hepatic cyst infection in all cases. Hepatic cyst infections occurring after (temporary) discontinuation of SDD were excluded.

Descriptive variables are expressed as n (%), median (range) or median (IQR). Pre- and post-SDD incidence was compared using the related-samples Wilcoxon signed-rank test for non-parametric distributions. Analyses were performed using IBM SPSS Statistics version 25 (SPSS Inc., Chicago, IL, USA).

Literature review

To investigate previously reported use of SDD to prevent recurrent hepatic cyst infection, we performed a literature search. We systematically searched PubMed (MEDLINE) and Ovid (Embase) from inception to 23 March 2020 (Table S1, available as Supplementary data at JAC Online).

Results

We identified eight PLD patients with a history of hepatic cyst infection who were exposed to SDD. Patient characteristics are described in Table 1. SDD regimens differed between patients (Table 1). Median SDD treatment duration was 20 months (range: 3–89 months).

Hepatic cyst infections

Benefit from treatment was evident in 75% (n = 6) of patients; 50% (n = 4) did not have any hepatic cyst infections during SDD treatment (Figure 1). In three cases, the episode-free period after introducing SDD was limited to 6 months, but during follow-up these cases had a numerically reduced frequency of infections. SDD was (temporarily) stopped seven times in six patients, because of adverse events (n = 3), development of antimicrobial resistance (n = 1) or as an experiment to validate continued effectiveness (n = 3). After cessation of SDD, five out of seven times (71%) a hepatic cyst infection developed shortly after discontinuation (median: 3 weeks, range: 1.5–6 weeks). SDD was reinitiated by the treating physician in three cases and was under consideration in another.

Cyst infections over time are shown in Figure 1. The incidence before SDD was 0.09 episodes per month (IQR: 0.06–0.25 episodes per month). Incidence during treatment was reduced to 0.01 episodes per month (IQR: 0.00–0.05 episodes per month). This 89% reduction was not significant (P = 0.12).

Adverse events

In total, 75% (n = 6) of patients suffered from adverse events that were probably SDD related (Figure 1). These were mild (Grade 1) in three cases and consisted of diarrhoea and/or nausea. Severe (Grade 3) adverse events occurred in two cases and consisted of: (i) recurrent oral/vaginal Candida infections requiring antifungal treatment and addition of nystatin; and (ii) severe progressive, irreversible perceptive hearing loss probably related to neomycin-induced ototoxicity. In one case, antibiotic resistance to polymyxin E in blood culture isolates of E. coli was documented during SDD treatment.

Table 1. Baseline characteristics; N = 8

| Characteristic                  | n | %  |
|--------------------------------|---|----|
| Age (years), median (IQR)      | 65 (51–74) |
| Centre, n (%):                 |   |    |
| Radboudumc                     | 5 (63) |
| LUMC                           | 3 (38) |
| Female, n (%)                  | 7 (88) |
| ADPKD, n (%)                   | 7 (88) |
| Renal transplant, n (%)        | 4 (50) |
| CKD stage >3, n (%)            | 5 (63) |
| Initial SDD regimen, n (%):    |   |    |
| polymyxin B/neomycin; 1 MIU/250 mg, 4×/day | 3 (38) |
| polymyxin E; 95 mg, 1×/day     | 3 (38) |
| polymyxin E/neomycin; 95/375 mg, 1×/day | 1 (13) |
| polymyxin E/tobramycin; 200/160 mg, 1×/day | 1 (13) |

MIU, million IU.
In another patient, loss of response after years of SDD use suggested development of antibiotic resistance, but this was not confirmed by microbiological testing.

**Literature search**

Our systematic search yielded 59 articles in PubMed (MEDLINE) and 116 in Ovid (Embase). After screening of titles and abstracts, no relevant publications were found (Table S1).

**Discussion**

Our observational data suggest that SDD reduces the incidence of recurrent hepatic cyst infection and show that recurrence occurs shortly after SDD discontinuation.

However, adverse events deemed related to SDD occurred in 75% of patients. Two events were graded severe, whereof one was irreversible hearing loss due to aminoglycoside ototoxicity. One case had proven resistance to polymyxin E and another was suspected because of loss of response. As patients were not regularly screened for antimicrobial resistance, total prevalence and impact remain unknown. Resistance to polymyxins and aminoglycosides usually does not influence future therapy as they are rarely used as therapeutic systemic antimicrobials in these patients.

Antimicrobial resistance and recurrence after cessation of SDD have been reported previously. A prospective study showed that post-ICU incidence of hospital-acquired infections tended to be higher in patients who had received SDD, which may be related to changes in gut colonization. This was supported by the finding that rebound of antibiotic resistance occurred upon withdrawal of SDD. By contrast, a meta-analysis did not show increase in resistance with SDD in ICUs. These conflicting results may stem from highly individualized effects on the gut resistome. Nevertheless, the societal impact of potential increased antimicrobial resistance should be considered before initiating SDD. In clinical practice, periodic surveillance of antimicrobial resistance should be considered for long-term SDD, especially for monotherapy.

We describe the experience in two Dutch referral centres, limiting generalizability. Several factors could have led to overestimation or underestimation of infection incidence. First, data may have been collected directly from patients by their physician. Second, some episodes were diagnosed as probable hepatic cyst infection without systematically excluding other causes of infection. We decided to use the treating physician’s diagnosis. Third,
we used resistance patterns to distinguish rapidly succeeding infection from persistent infections, as specific pathogen typing was not available. Fourth, the post-SDD infection incidence may be underestimated because the recurrence-free period until ‘present’ was included. All microbiological diagnostic procedures performed in Dutch clinical microbiology laboratories follow standardized procedures and have set performance standards for antimicrobial susceptibility tests. However, in view of the retrospective nature of this study, variations in pathogen identification and susceptibility testing between laboratories cannot be excluded.

Future studies are needed to corroborate these preliminary results. As there are only a few patients, conducting a randomized trial is not feasible. While crossover may reduce sample size, stopping SDD early may pose a serious risk of recurrence. Therefore, a study with fixed investigational products and a set follow-up duration before and after the start of SDD, with prospective assessment of efficacy, safety and antimicrobial resistance, is paramount.

To conclude, this proof-of-concept retrospective study shows a potential benefit of SDD prophylaxis in PLD patients suffering from recurring hepatic cyst infections. Despite the situation that SDD is associated with potentially severe adverse events, we recommend considering SDD in the management of recurrent cyst infection in these patients.

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Transparency declarations
None to declare.

Supplementary data
Table S1 is available as Supplementary data at JAC Online.

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