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Oral multispecies probiotic as adjunctive therapy for Clostridium difficile Infection: Case series involving 10 patients (5 of them with recurrent CDI)

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Background and Objective:

Evidence supporting the benefit of probiotics in Clostridium difficile Infection (CDI) treatment remains sparse. We report a descriptive case series of ten patients with CDI of a single university hospital (five different departments, Nov. 2010 to July 2011) who received adjunctive probiotic multispecies therapy (at least for 2 weeks). Five out of these suffered from recurrent and three from severe CDI.

Age group	Survived	Died	Causative	Contributive	Inconclusive	**% Causative + Contributive**
< 70	479	42	6	15	21	4.0
70-74	103	16	2	6	8	6.7
75-79	88	13	1	6	6	6.9
> 80	209	23	3	11	9	6.0

Table 3: Population characteristics of CDI cases at University Hospital Salzburg from 2009 to 2011

Material and Methods:

A new product was assembled consisting of the following 10 bacterial strains with a total dose of 10^9 cfu/g: B. bifidum W23, B. lactis W18, B. longum W51, E. faecium W 54, L. acidophilus W37 and W55, L. paracasei W20, L. plantarum W62, L. rhamnosus W71, L. salivarius W24 and a mixture of 5% amineral elements and 15% of Raftilose®synergy1 (enriched with inulin and oligofructose). To test whether the product was actually performing and no inhibitory effects were introduced by combining so many strains an observational study in elderly patients based on a detailed retrospective chart review was performed.

Case definition:
A patient was identified as a laboratory confirmed, symptomatic CDI patient who received adjunctive probiotic therapy at the time when oral metronidazol or vancomycin was initiated.
Cases were identified by quering surveillance data for laboratory proof of Clostridium difficile (toxigenic culture), consecutively followed by interviewing ward-staff by phone; retrospectively medical records were reviewed to ascertain clinical signs of CDI, therapy, medical history and outcome. On the basis of retrospective chart review all patients met the following critieria: Diarrhea, antibiotic treatment with metronidazole or vancomycin and multistrain probiotics.
Severe CDI and recurrent CDI was defined as described by Bauer et. al 2009 in CMI by clinical signs and confirming lab findings. Demographics and clinical data are shown in Table 1 and 2.
A follow up was done after six month.

Treatment description and definition of resolution:
Resolution was defined as no further laboratory signs of inflammation and/or fever, and reduction of stool frequency less than 3 times/24h for at least 72hours according to Bauer et al. 2009. For treatment details see Table 1 and 2.
A complementary epidemiological investigation was done out of the hospital CDI surveillance-system for both the period of the investigated cases and for the time period 2009 to 2011 (see table 3) to gain more background information of the local/hospital epidemiological situation.

Results:

As table 3 clearly shows the caseload of CDI is proportionally much higher in the group under 70 years of age, with 521 cases under 70 versus 452 in the group over 70. The proportion of *C. difficile fatal cases (*causative and contributive cases) was 21 (<70) over 29 (>70), 4% over 6.5% resp.
This clearly shows that the Salzburg cohort behaves like described in literature: relatively more CDI in older people and absolutely (and relatively) more deaths contributed to or caused by *Clostridium difficile* over 70 years. From this base line situation we selected the cases.

Treatment and outcomes:

The mean age of patients was 82 years (range 72-89); the majority were men (7 out of 10). All patients were hospitalized at the onset of CDI. Only one of the 10 patients had no history of antimicrobials; 9 of 10 received antimicrobial medication (range: 1 to 6, mean: 3.7 different antibiotics) in the last three months before onset of CDI. The most frequently administered antibiotics were ciprofloxacin and amoxicillin+clavulanic acid (each 5 of 9 patients) and piperacillin+tazobactam (4 of 9 patients). 8 patients got PPIs and/or cortison before and during the CDI-therapy. Four out of ten patients had received different single-strain probiotics before. All but one patient suffered from severe underlying diseases like malignancies, renal failure or chronic vascular diseases. [Table 1]
Six of ten patients showed fever; mean leukocyte count was 13,500, mean CRP was 13,7g/dl. In all patients, the CDI had been confirmed by laboratory results. Radiography and endoscopy brought no further useful information. [Table 2]

Complete resolution of clinical presentation occured in nine patients (90%), and one of the observed subjects died within a 3-months follow up period. This patient suffered from pneumonia which led to the fatal course. No adverse events were reported. A repeated stool testing was performed in 9 of 10 patients and these proofed to be negative. Molecular characterization of the strains was done in 70% (7 out of 10); PCR-ribotyping revealed thereby 5 different strains [Table 2]. No clustering or transmission was seen among the investigated patients.

Data from our surveillance system indicated 9 fatal courses directly related to CDI out of 151 cases (case-fatality ratio: 6%) during the observation period. 84 of the observed patients were males; the mean age was 67 (range: 19-94). None of the fatal cases had a documented treatment with any probiotics.

ID	Age	Sex	Underlying Disease	Primary CDI episode	Relapse 1	Relapse 2	Anti-microbials history	Cortico-steroids/PPI
1	88	m	CDI		x		None	PPI
2	89	f	Uterus carcinoma	x			unknown antibiotic, Ciprofloxacin	N
3	72	m	Glomerulonephritis			x	Ciprofloxacin, AmoxClav, Rifampicin, SulfTrim	Cortison
4	85	f	Epilepsia	x			Cefazolin, PipTaz	PPI
5	85	m	Bladder carcinoma			x	Ciprofloxacin, PipTaz, Ceftriaxon, SulfTrim, Vancomycin, AmoxClav	PPI
6	80	m	Bronchitis, recurrent UTI	x			Ciprofloxacin, Levofloxacin, SulfTrim	PPI
7	76	m	Renal replacement therapy	x			Ciprofloxacin, AmoxiClav, PipTaz	Cortison, PPI
8	79	m	Endocarditis, CDI		x		Clarithromycin, Moxifloxacin, Metronidazole	Cortison, PPI
9	81	m	Arterial occlusive disease (PAOD)	x			AmoxClav, Clarithromycin, Clindamycin, Ciprofloxacin, PipTaz	N
10	85	f	Sepsis, recurrent Erysipelas, recurr. CDI		x		AmoxClav, Meropenem, Metronidazole, Vancomycin, AmpSulbactam	PPI

Table 1: Demographic characteristics, underlying disease, manifestation of CDI (primary episode, first or second relapse) and riskfactors

Conclusion:

This case series shows that, even in patients at high risk, with multiple severe underlying diseases, restoration of a healthy colonic microbiota by administering multistrain probiotics might be beneficial as well by shortening the diseases course as, so far, preventing further relapses in patients with recurrent CDI. Furthermore this article comprises a theoretical and pratical basis to initiate well designed clinical trials to evaluate multistrain probiotic treatment in different CDI patient groups with different underlying diseases.

ID	Stool samples positiv for C. diff.	Repeated stool testing positiv for C. diff.	Ribotype	MTZ	V	V, oral Dosage+duration	MSP	MSP Dosage + duration of therapy	Probiotics history	Fever ≥ 38°C	Radiography (plain film, CT oder sonography)	Endoscopy	Leuco Count/ 1000	CRP g/dl	Clinical resolution
1	yes	No	023	yes	yes	4x125mg	yes	twice daily	SSP	yes	no	No	17,7	3	complete resolution but died of pneumonia three months later
2	yes	No	014	no	yes	4x125mg	yes	twice daily	no	no	yes, colon not described	No	8,98	6,4	complete
3	yes	No	413	yes	yes	4x125mg	yes	twice daily	no	yes	yes, colon not described	No	4,2	8	complete
4	yes	No	433	yes	yes	4x125mg	yes	twice daily	SSP	yes	no	No	12,66	15,1	complete
5	yes	No	014	yes	yes	4x125mg	yes	twice daily	MSP	yes	yes, CT: known radiogenic colitis	yes, aborted, bleeding and stenosis	11,4	20,3	complete
6	yes	No	nd	yes	yes	4x125mg	yes	twice daily	SSP	no	yes, colon not described	yes, no sign of enteritis	10,46	6,8	complete
7	yes	No	nd	yes	yes	4x125mg	yes	twice daily	no	no	no	No	12,11	16,86	complete
8	yes	No	053	no	yes	4x125mg	yes	twice daily	no	no	no	No	18,52	13,2	complete
9	yes	No	nd	yes	yes	4x125mg	yes	twice daily	SSP	yes	no	No	25,48	26,2	complete
10	yes	Nd	053	yes	yes	4x125mg	yes	twice daily	MSP	yes	no	No	13,45	20,9	complete

Table 2: Treatment, lab findings and outcomes; nd: not done; MTZ: metronidazole; V: Vancomycin (oral); MSP: Multistrain probiotic; SSP: Single strain probiotic