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SACCHAROMYCES BOULARDIIS EFFICASSY DURING ANTIBIOTICOTHERAPY AND IN CLOSTRIDIUM DIFFICILE DISEASE
EFIKASITETI I SACCHAROMYCES BOULARDII GJATE ANTIBIOTIKOTERAPISE DHE NE SEMUNDJEN E CLOSTRIDIUM DIFFICILE

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PERMBLEDHJE
Perdorimi i antibiotikeve eshte nje fenomen mjaft i perhapur ne praktiken mjekesore dhe ne gjendje te tilla si diarrene qe shoqeron antibiotiket,colitin e shkaktuar nga clostridium difficile tregon nje ndikim te qarte ne cilesine e jetes. Ne synojme te sjellim nje evidence te re mbi efikasitetin e trajtimit per diarene nga antibiotiket dhe superioritetin e kombinimit : metronidazole+sacharomyces boulardii kundrejt monoterapise me Metronidazole per trajtimin e colitit te shkaktuar nga antibiotikoterapia. Individet e perfshire ne studim ishin paciente te hospitalizuar ose nen trajtim me antibiotikoterapi te cilet provuan diarre tri dite pas fillimit te antibiotikoterapise deri dhjete dite pas perfundimit te antibiotikoterapise. U vleresua dhe siguria e trajtimit. Terapia e kombinuar u paraqit superiore ne :Reduktimin e kohezgjatjes te simptomove klinike te colitit, nje perqindje me te larte te rasteve me remision klinik, pakesim te normes te rekurencave. Si konkluzion ne evidentuam se terapia e kombinuar eshte superiore per efikasitetin e saj kundrejt monoterapise dhe mjaft e sigurte per tu perdorur ne praktiken mjekesore.
Fjalët çelës: Sacharomyces boulardii, Diarreja, Antibiotikoterapi, Colitis, Clostridium difficile

SUMMARY
Antibiotic usage is a widespread fenomena in the medical practice and in such conditions like antibiotic associated diarrhea, colitis disease caused by clostridium difficile show an evident impact in life quality.We tend to bring up a new evidence over the efficacy of treatement for antibiotic associated diarrhea and the superiority of the combination: metronidazole+sacharomyces boulardii over Metronidazole monotherapy for the treatemen of colitis disease triggered by antibioticotherapy. People included in the study were hospitalized patients or not under antibioticotherapy treatment that experienced diarrhea three days after antibioticotherapy initiation till ten days after antibioticotherapy completion. Safety of treatment was also assessed. Combined therapy was demonstated superior in: Reducing the timing of colitis clinical symptoms,a higher percentage of cases with clinical remission, decreasing the rate of recurrences. In conclusion we found that combination therapy is superior in terms of efficacy over monotherapy and safe enough to be used in medical practice.
Key -words: Sacharomyces boulardii, Diarrhea, Antibioticotherapy, Colitis disease, Clostridium difficile.

INTRODUCTION

Antibiotic associated diarrhea(AAD)
is considered as an inexplicable diarrhea that happens in association with antibiotic administration. The rate of this situation varies among antibacterial agents.Diarrhea happens approximately at 5-10 % of patients treated with ampiciline,10-25% of those treated with amoxicillin- clavulonate, 15-20%of those that take cefixime and 2-5 % of those that undergo

treatment with ceffalosporins, fluorquinolone, azithromycine, clarithromycine,
erythromicine and tetracycline. The rate of diarrhea associated with parenteral administration of antibiotics especially those with enterohepatic circulation are similar with agents administered orally.

The specter of findings at antibiotic associated diarrhea vary from a simple diarrhea that is defined as frequent watery stools without other complications, till to colitis disease that is a potential source of serious progressive disease.
The clinical appearance of antibiotic associated colitis include:Abdominal cramp, Fever, Leucocytosis, Fecal leucocytosis, Hypoalbuminemia.Although the CD (clostridium difficile) infection accounts for only 10-20% of cases with antibiotic associated diarrhea, it is responsible for the most cases of antibiotic therapy colitis.AAD may be caused by other enteropathogens,through:
1-direct effect of antimicrobial agents in the intestinal mucosa,
2- metabolic consequences of altered colonic flora.
Other enteropatogens that may cause diarrhea include: salmonella ,clostridium perphringens type A , staphylococcus aureus and probably candida albicans. The distinction is important because metronidazole is effective for CD but not for the infection caused by staphylococcus aureus.Drugs have multiple effects in the gastrointestinal tract despite of antimicrobial activity.Erithromycine acts as agonist of motilin receptors and accelerates gastric evacuation.
Clavulonate in amoxicilline-clavulonate stimulate intestinal motility. Penicillin may cause segmental colitis. Antibiotics may substantially reduce the concentration of fecal anaerobes that normally are present in colon. As a consequence carbohydrates metabolism may be reduced, what cause osmotic diarrhea. Also the primary biliary acids breakdown which are potential colonic secretors agents may be reduced.
Risk factors include: advanced age,prolonged hospitalization, exposure to antibiotics.

Clostridium difficile is a gram positive, anaerob, sporforming bacili responsible for diarrhea development and colitis with clinical appearance by antibiotics. Infection from CD usually is manifested like a mild to moderate diarrhea and sometimes with abdominal cramps. Pseudomembranes (adherent yellow to white plaques, in the intestinal mucosa are noted rarely. At rare cases of CD infection patients may represent acute abdomen and life threatening, fulminate colitis. Approximately 20% of hospitalized people get CD during hospitalization, and more than 30% of these patients develop diarrhea.Therefore colitis by CD is actually one of the most frequent nosocomial infections.

- Pathphysiology

Colitis by CD result from disorders of normal bacterial colonic flora , colonization with CD, and the release of toxins that cause inflammation and mucosal damage. Antibioticotherapy is the main factor that alterate colonic flora. Hospitalized patients are the primary target for infection by CD.CD is present at 2-3% of healthy adults and at 70% of healthy children. Treatment of asymptomatic carriers is not recommended. Colonization happens through oro-fecal route .
Normal flora of colon is resistant to the colonization and CD overgrowth. The use of antibiotics that suppress the normal flora of the colon , helps proliferation of CD. Pathogenic species of CD produce two toxins , A and B. Toxin A is an enterotoxine, and toxine B is a cytotoxine. Both of toxins A and B seems to play a role in colitis pathogenesis from CD at humans.

- Epidemiology

CD infection mainly happen at hospitalized patients causing approximately 3 million cases of colitis diarrhea per year in USA. According to McFarland et al 7% of hospitalized patients and 28% of patients that were discharged from hospital(that were treated) had positive culture for CD.The incidence of CD at hospitalized patients has seen growth from 30-40/100000 in 1990,to 84/100000 in years 2005. According to another report, only 20000 cases/year are diagnosed as outpatients.

- Morbidity/mortality

While too many patients with CD colitis recover without specific therapy, symptoms may be present and complicate. Diarrhea by CD may be a serious situation with mortality till to 25% at the elderly and in patients with serious diseases. Mortality has been growing in the last decade reflecting an increase in the virulence of CD species, especially the strain NAP1/027. Colonization with CD results in a wide clinical spectrum, from asymptomatic carriers , to mild self limited diarrhea, pseudomembranous colitis, till to fulminate colitis. Most of patients develop diarrhea during or shortly after beginning of antibiotics. However 25-40% of patients may be asymptomatic even for 10 weeks after taking antibiotics.Symptoms include:

Watery mild to moderate diarrhea that rarely is associated with blood,Cramp form abdominal pain,Anorexia ,General situation altered

Fevers, especially in aggravated cases.

At people over 60 years old the incidence of a positive test for toxins of CD is 20-100 time higher than at 20 years old.Diagnostic tests

Findings that have been considered nonspecific but suggestive for infection by CD include:

Leucocytosis, Hypoalbuminemia, Leucocytes in stools. Histological findings in colon vary from normal to pseudomembranous colitis.

Abdominal X-Ray, CT and colonoscopy may be helpful in detection of infection by CD, but these methods are nonspecific, no sensitive and often expensive, so they are totally substituted from the test for CD toxins. The test of cytotoxine that uses tissue cultures has been the gold standart for the diagnose. Enzyme immunoassays (EIA) with reagent for both toxins A and B are today in use with high specificity but with false negative of 10-20%.

- Treatment

Mild to moderate self limited cases may not need treatment. It is indicated treatment with Metronidazole or Vancomycine when there is clinical evidence of colitis, and positive test for toxins of CD. Metronidazole 500 mg/three times/day, or 250mg/four times/day. Vancomycine 125mg/four times/day. Time of treatment duration is 10 days. Efficacy 90-97%. Treatment usually is given orally.Metronidazole may be used i/v, while vancomycine is used only orally. Antiperistaltyc agents as : loperamid, and opiate should be avoided.Sacharomyces boulardii for reconstitution of normal colonic flora or enema with human stools for the same purpose. IgG against toxin A. Relapse after treatment may happen in 20-30% of cases, which needs retreatment.

- The study

The study included 78 adult patients aging from 20-70 years old which have been hospitalized or not and that three days after the beginning of antibiotic therapy and till to 10 days after it was completed have experienced watery diarrhea with more than 3-4 non hemorrhagic episodes, clinically associated with symptoms of colitis. Patients should not have other concomitant conditions as: Diabetes mellitus,Gastrectomy or colectomy ,Thyroid or other concomitant metabolic diseases,Neoplasi,Viral situations

Patients should not have used at least three months drugs such:Laxatives,Antiacides,

Contrast agents,NSAID

Products that contain lactose ,sorbitol

Cholinergic agents

Immunossupresore drugs,Chemotherapy.

Patients were divided in two groups of 39 patients each one. At the first group were included patients that were treated with the combination Metronidazole 250mg/four times daily and sacharomyces boulardii 250 mg/two times daily with surveillance follow-up of four weeks. The second group included patients that were treated only with metronidazole 250mg/four times daily and with surveillance follow-up of four weeks.From the clinical surveillance of the patients resulted that at the third day of therapy at the first group GR-I it was achieved remission in 27 patients compared to 22 patients of the GR-II second group.Seventh day it was achieved remission in 33 patients of GR-I, compared to 30 patients of GR-II, and at day 10, patients remission at each group was identical to that of day 7. At the end of therapy remission at the group of patients with combined therapy

metronidazole+sacharomyces boulardii was achieved at the rate 84.6%, while at the group of patients with monotherapy(only metronidazole) at the rate 76.9%. Analyzing these data results that in combination therapy clinical remission was achieved earlier in time and at a higher percentage demonstrating the superiority of combined therapy.

Tab. 1-Division of patients for each group by age.

The age at years	Patients number	20-30	30-40	40-50	50-60	60-70
Gr - I	39	8	5	9	11	6
Gr - II	39	7	10	11	7	4

Tab.2-Clinical remission at the third, seventh, tenth day and the percentage of therapis efficassy for each group.

	Patients	Patients with clinical remission within three days	Patients with clinical remission within seven days	Patients with clinical remission within ten days	Remissions percentage
Gr-I	39	27	33	33	84.6%
Gr-II	39	22	30	30	76.9%

Tab. 3-Side effects noted at each group.

Side effects	Number of patients	Nausea	Excessive thirst	Constipation
Gr I	39	6	5	3
Gr II	39	7	4	1

Considering side effects it was noted a light difference in constipation between both two groups, respectively 3 cases for group I and 1 case for group II, but this was resolved by the end of therapy.

Tab. 4-Relapses percentage of diarrhea after treatment with respective therapy for each group

	Number of patients	Follow-up for 4 weeks	Symptoms recurrence	Relapses percentage
Gr I	39	34	6	17.6%
Gr II	39	36	12	33.3%

In the follow-up period for 4 weeks after therapy

contacts were lost with 5 patients at the GR-I and three patients at the GR-II because they missed contacts.Also evaluating relapses of diarrhea and its associated symptoms 4 weeks after therapy

- **RESULTS**

Sacharomyces boulardii efficassy was obvious in:

-Reducing the time of colitis symptoms caused by antibioticotherapy

-A higher number of cases with clinical remission by a combined therapy than by monotherapy.

-Decreasing the percentage of recurrences

While there was no significant differences between two groups in nausea and excessive thirst, and this showed that the safety of the preparation is good enough.

results that relapse was at the rate 17.6% at the GR-I, versus 33.3% encountered at GR-II

which demonstrates that even in the prevention of relapse of diarrhea ,combined therapy is superior to monotherapy.

CONCLUSIONS

Combined therapy metronidazole+sacharomyces boulardii is more effective and with the same rate of safety as metronidazole monotherapy in the diarrhea caused by antibiotics and associated colitis, as well as in prevention of recurrences.

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